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(71)Applicant : TAKEDA CHEM IND LTD
(72)Inventor : AONO TETSUYA
OOKAWA SHIGENORI
DOI TAKAYUKI

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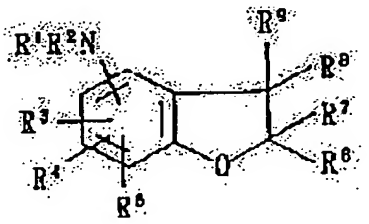
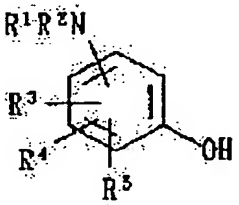
(54) AMINOCOUMARAN DERIVATIVE

(57)Abstract:
PURPOSE: To obtain a new compound having action for suppressing production of peroxide lipid and action for inhibiting and suppressing production of lipoxygenase and HHT and useful for treatment and prevention of circulatory disease, inflammation and allergic disease.
CONSTITUTION: A compound of formula I (R1 and R2 are H, acyl, alkoxycarbonyl, etc.; R3 to R5 are OH, amino, etc.; R6 and R7 are aliphatic, etc.; R8 and R9 are H, aromatic ring, etc.), e.g. 5-amino-2-benzyl-2,4,6,7-tetramethyl-2,3-dihydrobenzofuran. The compound of formula I is obtained by condensing a compound of formula II to a compound of formula III (CH2R1 is a group corresponding to R6) and then as necessary, carrying out deprotection, acylation and alkylation reaction, respectively or in the combination of two or more reactions thereof.



I



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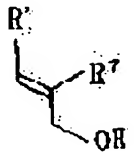

III

LEGAL STATUS

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* NOTICES *

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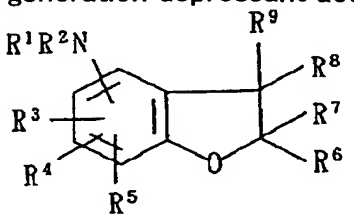
2.**** shows the word which can not be translated.
3.In the drawings, any words are not translated.

DETAILED DESCRIPTION

[Detailed Description of the Invention]
[0001]
[Industrial Application] This invention relates to the physic constituent which makes an active principle a new amino coumarane derivative or its salt, and this. It is related with the peroxylipid generation inhibitor which makes an active principle the new amino coumarane derivative which has new peroxylipid generation depressant action useful as still more detailed prevention / therapy agents of various diseases, such as arteriosclerosis, liver disease, and cerebrovascular disease, or its salt, and it.
[0002]
[Description of the Prior Art] The application to the physic of the antioxidation and a peroxylipid generation inhibitor has come to be variously tried as it becomes clear that the radical reaction incidental to generation and it of the peroxylipid in the inside of the body has various bad influences on a living body through a film failure, an enzyme failure, etc. the peroxylipid generation inhibitor used in current and a physic field -- mainly -- the derivative of natural anti-oxidants, such as vitamin C and vitamin E, and a phenol derivative -- it is (Kenji Fukuzawa work, 46 Japanese clinical one, 2269-2276 pages (1988)) -- an operation cannot be weak, a side effect cannot occur, or it cannot necessarily be satisfied practical. Moreover, as an amino coumarane derivative, JP,60-132977,A (application: intermediate field of a useful as prevention / therapy agent of disease of the coronary circulatory system 2 and 2'-iminobis ethanol derivative), JP,60-169473,A (application: antemetic, antipsychotic drug), JP,62-234083,A (application: antemetic, antipsychotic drug), JP,64-38090,A (application: remedy of diabetes mellitus, its complication, and hyperlipidemia), Patent Publication Heisei No. (application: antemetic) 501226 [one to], and U.S. Pat. No. 4,772,730 (application: pyrazoline insecticide) are known conventionally. However, it has two aliphatic series radicals which may have four specific substituents in the benzene ring of amino coumarane, and may have the substituent in the 2nd place of amino coumarane, among those the amino coumarane derivative whose alpha position of at least one is a methylene group was not compounded at all conventionally. The main purpose of this invention is to offer the peroxylipid generation inhibitor which makes an active principle the new molecular entity which has the outstanding peroxylipid generation depressant action, its industrial advantageous manufacturing method, and it.
[0003]
[Means for Solving the Problem] In order to solve said technical problem, this invention persons compounded many new molecular entities, and investigated antioxidation activity and peroxylipid generation depressant action about each. consequently, a general formula [I] -- [Formula 7]



the inside of [type, and R1 and R2 are the same — or — differing — a hydrogen atom and an acyl group — An alkoxy carbonyl group, the aliphatic series radical which may have the substituent, respectively, or a ring radical R3, R4, and R5 The same or the hydroxyl group which may be differed and acylated, the amino group which may have the substituent, respectively, The carbon isocyclic ring in which it is an alkoxy group or an aliphatic series radical, or two of R3, R4, and R5 may have the substituent may be formed. R6 and R7 It is the same or the aliphatic series radical which may differ and may have the substituent, and, moreover, the alpha position of at least one of R6 and the R7 is a methylene group. R8 and R9 While succeeding in the invention of the same, the amino coumarane derivative of the new structure expressed with] which differs and shows a hydrogen atom, the aliphatic series radical which may have the substituent, respectively, or a ring radical, or its salt These new molecular entities completed [having an operation useful as physic, such as powerful peroxylipid generation depressant action,] this invention for examination in piles to the header and the pan.

[0004] That is, this invention offers the physic constituent which makes an active principle the new amino coumarane derivative expressed with said general formula [I], its salt, and it.

[0005] In a general formula [I], carboxylic-acid acyl, sulfonic-acid acyl, etc. are mentioned as an acyl group expressed with R1 and R2. As carboxylic-acid acyl, the alkyl sulfonyl groups and phenyl sulfonyl groups of carbon numbers 1-3, such as a methane sulfonyl, an ethane sulfonyl, and a propane sulfonyl, are mentioned as the acyl groups (an example, the formyl, acetyl, a propionyl, the butyryl, isobutyryl, valeryl, etc.) of carbon numbers 1-6, and a sulfonic-acid acyl group. As an alkoxy carbonyl group expressed with R1 and R2, the low-grade alkoxy carbonyl group of the carbon numbers 1-5 of ARUKOKISHI, such as a methoxycarbonyl group and an ethoxycarbonyl radical, is mentioned.

[0006] The aliphatic series radical expressed with R1 and R2 may be a radical of saturation, or may be a radical of partial saturation, for example, an alkyl group, an alkenyl radical, and an alkynyl group are mentioned. The shape of a straight chain, the shape of branching, and annular are sufficient as this alkyl group. A with a carbon number of about one to six low-grade alkyl group is suitable among these alkyl groups, for example, methyl, ethyl, propyl, i-propyl, butyl, i-butyl, t-butyl, pentyl, hexyl, cyclo propyl, cyclo butyl, cyclopentyl, etc. are mentioned. Moreover, as an alkenyl radical expressed with R1 and R2, generally the thing of carbon numbers 2-6 is desirable, for example, an allyl compound, propenyl, i-propenyl, 2-butenyl, 2, 4-swine dienyl, 2-pentenyl, etc. are mentioned. Moreover, as an alkynyl group expressed with R1 and R2, the radical of carbon numbers 2-6 is desirable, for example, generally ethynyl, 2-propynyl, etc. are mentioned.

[0007] As long as it is the radical which does not limit especially as a substituent which these aliphatic series radicals may have, and is usually used for physic, what kind of thing may be used. Specifically For example, hydroxyl;C1-3 alkoxy (for example) [methoxy,] [ethoxy **] ;, such as n-propoxy or iso-propoxy, — aralkyloxy (one to phenyl-C6 alkyloxy, or naphthyl-C — one to 6 alkyloxy) For example, benzyloxy one, phenethyloxy, etc.; Aryloxy (For example, phenyloxy, naphthyloxy one, pyridyloxy, IMIDAZORIRUOKISHI, etc.); mercapto; — C1-3 alkylthio A;C1-3 alkyl sulfonyl (For example, a methylthio or ethyl thio etc.) ;C1-3 alkyl sulfinyl (For example, a methyl sulfonyl or an ethyl sulfonyl etc.) (For example, methyl sulfinyl or ethyl sulfinyl etc.); aralkyl thio (one to phenyl-C6 alkylthio, or naphthyl-C — one to 6 alkylthio) for example,; aralkyl sulfonyls (a phenyl-C1-6 alkyl sulfonyl or a naphthyl-C1-6 alkyl sulfonyl —), such as benzyl thio and phenethyl thio for example,; aralkyl sulfinyls (phenyl-C1-6 alkyl sulfinyl or naphthyl-C1-6 alkyl sulfinyl —), such as a benzyl sulfonyl and a phenethyl sulfonyl For example, benzyl sulfinyl, phenethyl sulfinyl, etc.; Aryl thio ; An aryl sulfonyl (For example, phenylthio, naphthyl thio, pyridyl thio, imidazolyl thio, etc.) ; Aryl sulfinyl (For example, a phenyl sulfonyl, a naphthyl sulfonyl, a pyridyl sulfonyl, or an imidazolyl sulfonyl etc.) (For example, phenyl sulfinyl, naphthyl sulfinyl, pyridyl sulfinyl, or imidazolyl sulfinyl etc.); amino; — C — one to 3 alkyl An aralkyl (one to phenyl-C6 alkyl, or one to naphthyl-C6 alkyl), Monochrome or JI permutation amino permuted by 1 of aryls (phenyl, naphthyl, pyridyl, or imidazolyl) thru/or two pieces (For example, methylamino, ethylamino, dimethylamino, benzylamino, phenylamino, pyridylamino, etc.); halogen (for example, chloro or fluoro); — esterification carboxy [— for example Two to C2-5 alkoxy carbonyl

(methoxycarbonyl or ethoxycarbonyl)];C3 acyl Two to;C3 acyloxy (For example, acetyl, a propionyl, etc.) A;C2-3 acyl amide (For example, acetoxy, propionyloxy, etc.) Two to;C5 alkoxycarbonylamino (For example, acetamide etc.) (For example, methoxycarbonylamino or ethoxycarbonylamino etc.); — annular — amino-groups (for example, pyrrolidino, morpholino, piperazino, etc.); carboxyl group; — a carbamoyl group etc. is mentioned. The number of these substituents has 1-2 desirable pieces.

[0008] A phenyl group is mentioned as a ring radical expressed with R1 and R2. As a substituent on a phenyl group, the acyl group of the low-grade alkoxy ** carbon numbers 2-5 of the monochrome permuted by the amino group and the low-grade alkyl group of carbon numbers 1-3 or a dialkylamino radical, a halogen, nitroglycerine, sulfo, cyano ** hydroxy ** carboxy, the low-grade alkyl of carbon numbers 1-5, and carbon numbers 1-3, the low-grade alkyl sulfhydryl group of carbon numbers 1-3, etc. are mentioned, for example. Although especially the number of substituents is not limited, the number of desirable substituents is 1-3.

[0009] - Although the radical expressed with NR one R2 may be permuted by which location on the benzene ring of coumarane, what is permuted by the 5th place of coumarane is good preferably. One side is a hydrogen atom and the alkyl group of the shape of a hydrogen atom, a phenyl group, or a straight chain, the shape of branching, and the annular carbon numbers 1-6 has [R1 and R2] desirable another side.

[0010] When the hydroxyl group expressed with R3, R4, and R5 is acylated, as the acyl group, the straight chain of carbon numbers 2-5 or branching-like carboxylic-acid acyl groups (for example, acetyl, a propionyl, butyryl, isobutyryl, etc.) are mentioned. When the amino group expressed with R3, R4, and R5 has a substituent, as the substituent, the aliphatic series radical or ring radical which is expressed with R1 and R2 and which may have the substituent, respectively is mentioned.

[0011] As an alkoxy group expressed with R3, R4, and R5, the alkoxy group which consists of an alkyl group of the shape of the shape of a straight chain of carbon numbers 1-6 and branching or an annular alkyl group is mentioned, and the monochrome permuted by the amino group and the low-grade alkyl group of carbon numbers 1-3 or a dialkylamino radical, a halogen, a hydroxy ** low-grade alkoxy ** low-grade alkyl sulfhydryl group, etc. are mentioned as a substituent which an alkoxy group has, for example.

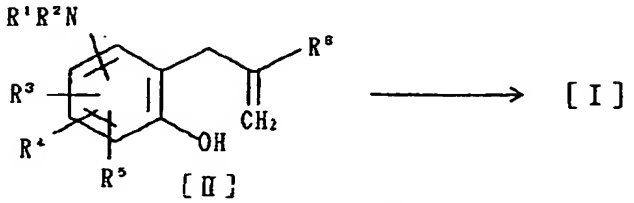
[0012] The substituent which the aliphatic series radical and aliphatic series radical which are expressed with R3, R4, and R5 may have applies to the aliphatic series radical expressed with R1 and R2.

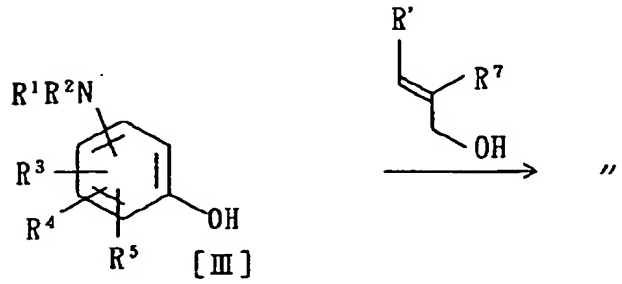
[0013] Moreover, two of R3, R4, and R5 may form the carbon isocyclic ring which may have the substituent, and its carbon isocyclic ring of 5 or 6 members is desirable in this case. As the substituent, the alkyl group of carbon numbers 1-3, the alkoxy group of carbon numbers 1-3, a hydroxyl group, etc. are mentioned. R3, R4, and R5 have the desirable alkyl group of the shape of a straight chain, the shape of branching, and the annular carbon numbers 1-6.

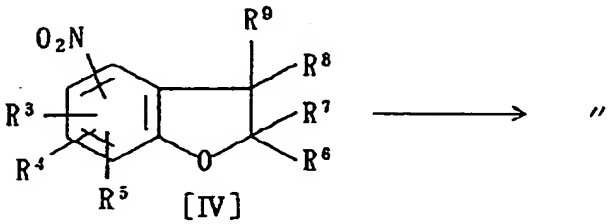
[0014] The aliphatic series radical expressed with R6 and R7 is the same as the case of R1 and R2, and the ring radical by which the substituent which the aliphatic series radical expressed with R6 and R7 has may be permuted besides the substituent of the aliphatic series radical expressed with R1 and R2 is contained. As the ring radical which may be permuted, and a substituent, the ring radical and substituent which are expressed with R1 and R2 are mentioned.

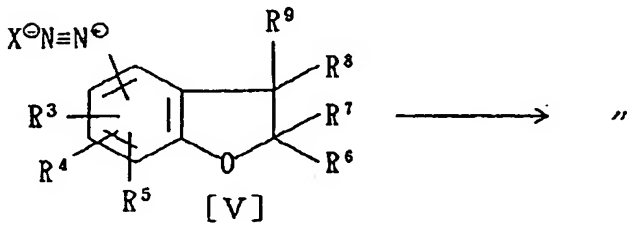
[0015] Furthermore, the alpha position of at least one of R6 and R7 is a methylene group. That is, in other words, R6 and R7 are the aliphatic series radicals which may be permuted, and at least one is a formula. - The radical expressed with CH2R' [R' shows among a formula the radical which forms the aliphatic series radical which may be permuted with hydrogen or -CH2] is shown. It is expressed with R'. - The substituent which the aliphatic series radical in the radical which forms the aliphatic series radical which may be permuted with CH2, and its aliphatic series radical have applies to the radical expressed with R6 and R7. One side is the alkyl group of the shape of a straight chain, the shape of branching, and the annular carbon numbers 1-6, and R6 and R7 have desirable alkyl group or aralkyl radical (one to phenyl-C6 alkyl or one to naphthyl-C6 alkyl is desirable, for example, they are benzyl, phenethyl, or phenylpropyl) of the shape of a straight chain by which another side may be permuted by the radical which has 1-5 hetero

atoms (N, S, O), the shape of branching, and the annular carbon numbers 1-6. As a radical which has these 1-5 hetero atoms, for example, C1-3 alkoxy ** aralkyloxy, aryloxy, one to C3 alkylthio, a C1-3 alkyl sulfonyl, C1-3 alkyl sulfinyl, aralkyl thio, an alkyl sulfonyl, aralkyl sulfinyl, aryl thio, an aryl sulfonyl, aryl sulfinyl, monochrome or JI permutation amino (amino permuted by 1 of one to C3 alkyl, an aralkyl, and aryl thru/or two pieces), and the annular amino group are mentioned.
[0016] The aliphatic series radical expressed with R8 and R9 is the same as the case of R6 and R7, and the ring radical expressed with R8 and R9 is the same as the case of R1 and R2. One side is a hydrogen atom and R8 and R9 have the desirable alkyl group of the shape of the phenyl group by which another side may be permuted by the alkyl group of the shape of a hydrogen atom, a halogen, or a straight chain, the shape of branching, and the annular carbon numbers 1-6, or a straight chain, the shape of branching, and the annular carbon numbers 1-6.
[0017] in addition, the compound shown by the general formula [I] — the class of substituent — although a stereoisomer arises depending on how — these isomers — independent — it does not come to see but those mixture is also contained in this invention.
[0018] As a salt of the compound expressed with a general formula [I], preferably, it is the salt permitted on physic and organic acids, such as inorganic acids, such as halide acid (an example, a hydrochloric acid, hydrobromic acid), a phosphoric acid, and a sulfuric acid, and an organic carboxylic acid (an example, oxalic acid, a phthalic acid, a fumaric acid, maleic acid), a sulfonic acid (an example, methansulfonic acid, benzenesulfonic acid), are mentioned as an example of the salt permitted on physic. Moreover, when a compound [I] has acidic groups, such as a carboxyl group, as a substituent, an inorganic base salt with alkali metal (an example, sodium, potassium) or an alkaline earth metal (an example, magnesium) and a salt with an organic base (amines, such as example, dicyclohexylamine, triethylamine, 2, and 6-lutidine) are mentioned. Hereafter, the compound expressed with a general formula [I] and its salt are named a compound [I] generically.
[0019] The compound [I] of this invention can be manufactured by the approach of a reaction formula -1.
Reaction formula -1 [Formula 8]









[-- X shows a halogen, and HSO4 or NO3 for the radical to which -CH2R' corresponded the above and this meaning with above R6 in R1, R2, R3, R4, R5, R6, R7, R8, and R9 among a formula.] [0020] That is, a ring closure is further carried out under existence of a base by request, carrying out a ring closure under existence of a base by request further, a compound [I] carrying out the ring closure of the compound [II] under existence of an acid by request, or using a halogen molecule, and manufacturing, or using a peroxy acid, and it manufactures. Furthermore, the chain extension and substituent exchange reaction by a deprotection reaction, the acylation reaction, the hydrogenation reaction, oxidation reaction, and the BITTIHHI (Wittig) reaction are compoundable independent or by carrying out or more [the] combining two respectively with a request. Moreover, a compound [I] can be manufactured that an allyl alcohol derivative and a suitable acid catalyst carry out bottom condensation of existence of the phenol [III], or by returning a nitro compound [IV] and a diazo compound [V], and can be further compounded [give / independent or / of a deprotection reaction, an acylation reaction, and an alkylation reaction / the reaction which combined two or more / the] by request. The inside of the above-mentioned reaction formula, R' - The radical shown by C= is changed into R6 of a compound [I] by the reaction with a compound [III]. That is, R' is a radical which forms R6 with -CH2-. As a halogen expressed with X, a base and a bromine are mentioned among a compound [V]. [0021] Among proton acid water solutions, such as a hydrochloric acid and a hydrobromic acid, the ring closure reaction by the acid is made to react at room temperature -150 degree C, or it is hydrogen chloride gas, boron-trifluoride etherate (BF3andEt2O), etc. among a suitable organic solvent (an example, chloroform, toluene, etc.), and it is performed by making it react at -5 degrees C - 150 degrees C. The ring closure reaction by the halogen is performed using a bromine etc. by making it react at -5 degrees C - 100 degrees C under existence of bases, such

as sodium acetate or triethylamine, by request among organic solvents, such as halocarbons (an example, chloroform, methylene chloride, etc.) or an acetic acid. A request performs the ring closure reaction by the peroxy acid at -10-50 degrees C under existence of bases, such as triethylamine, among organic solvents, such as a methylene chloride, using peroxy acids, such as m-chloro perbenzoic acid.

[0022] Moreover, the Friedel Kraft reaction of a phenol derivative and an allyl alcohol derivative is performed at 0-150 degrees C under existence of a sulfuric acid, trifluoro methansulfonic acid, and boron-trifluoride ETORATO among organic solvents, such as a dichloroethane.

[0023] The contact hydrogenation for which reduction of a nitro compound used the catalyst of palladium carbon etc., Under existence of acids (for example, a hydrochloric acid, an acetic acid, etc.) or bases (for example, sodium hydroxide etc.), Reduction by the titanium trichloride etc. can perform under existence of acids, such as reduction, an acetic acid, etc. using metals, such as iron, zinc, and tin. Moreover, reduction of a diazo compound It can carry out by processing at 0-100 degrees C among water or an organic solvent with the same hydrogenation reaction and reducing agents, such as sodium-hydrosulfite sodium. A request performs oxidation reaction at -78 degrees C - 25 degrees C among organic solvents, such as a methylene chloride and an acetone, under existence of bases, such as triethylamine, using dimethyl sulfoxide and oxidizing agents obtained from an oxalyl chloride, such as an oxidizing agent and a chromium trioxide.

[0024] When performing an addition-elimination reaction (BITTIHHI reaction), it carries out in solvents, such as dimethylformamide, a tetrahydrofuran, and dimethoxyethane, using sodium hydride, a sodium hydroxide, sodium alcoholate, n-butyl lithium, a lithium diisopropyl amide, etc. as a base, reaction temperature is -78 degrees C - 80 degrees C, and reaction time is about 0.5 to 24 hours. Moreover, when hydrogenating a double bond, according to a conventional method, the purpose compound can be obtained using the catalyst of palladium carbon etc.

[0025] Although desorption (hydrolysis) of the protective group of a hydroxyl group can be performed on the usual ester hydrolysis conditions, in being unstable, when a product reacts under an argon ambient atmosphere to oxygen under basic conditions, the target hydrolyzate can be obtained with good yield. Acylation will be performed by making it react under existence of base catalysts (preferably sodium hydride, potassium carbonate, a pyridine, triethylamine, etc.) or acid catalysts (an example, a sulfuric acid, hydrogen chloride, etc.) and in an organic solvent (an example, dimethylformamide, an acetone, tetrahydrofuran), if desired acylating agents (an acid anhydride, acid halide, etc.) are required. Reaction temperature is [about]. -10 to 100 degrees C and reaction time are 15 hours from about 10 minutes. In performing substituent exchange reaction, it carries out by making an amine, a thiol, alcohol, etc. react to 2-halo methyl -2 and the 3-dihydrobenzofuran derivative which carried out the ring closure at -5 degrees C - 200 degrees C in organic solvents, such as a non-solvent or dimethylformamide, and toluene, using bases (sodium hydride etc.) if needed with a halogen. As a reaction container, an autoclave is used if needed. Alkylation of the amino group and a hydroxyl group etc. is mentioned as an example of an alkylation reaction. Alkyl halide (as a halogen, they are chlorine, a bromine, and iodine), the alkyl ester of a sulfuric acid or a sulfonic acid, the alkyl ester of phosphorous acid, etc. are used for alkylation. An alkylating agent is performed by 1 - 2 double **********, and a reaction is usually performed under existence (an example, triethylamine, pyridine, etc.) of inorganic bases (an example, a sodium hydroxide, a potassium hydroxide, potassium carbonate, sodium carbonate, etc.) and an organic base. Although especially the solvent used at this time is not limited, organic solvents and water, such as a tetrahydrofuran, dioxane, dimethylformamide, and dimethylacetamide, are used. A reaction is usually performed at room temperature -100 degree C. the raw material compound [II] of this invention, [III], [IV], and [V] -- an approach given in a ****** 62-No. 502333 official report, and the very thing -- it can manufacture by the well-known approach or the approach shown in the after-mentioned example of reference.

[0026] The compound (I) obtained in this way can be isolated with the usual separation / purification means (an example, an extract, a chromatography, recrystallization, etc.). In addition, when a compound (I) exists as a diastereomer, each can be isolated with said separation / purification means by request. Moreover, when a compound (I) is the optically active substance, the usual optical-resolution means can separate into d bodies and l bodies.

[0027] the compound [I] of this invention — polyunsaturated fatty acid (linolic acid and gamma-linolenic acid —) A metabolic turnover improvement of alpha-linolenic acid, an arachidonic acid, dihome-gamma-linolenic acid, and eicosapentaenoic acid, The operation (antioxidation operation), the example of 5-lipoxygenase system metabolite [which control a peroxylipid generation reaction especially, Leukotrienes, 5-hydroperoxyeicosatetraenoic acid (HPETE), 5-hydroxyeicosatetraenoic acid (HETE) and RIPOKISHIN It has a circulatory system improvement operation and antiallergic operation of the generation depressant action of], such as leukotoxins, the inhibitory action of thromboxane-A2 synthetic enzyme, a prostagladin I2 synthetic-enzyme maintenance promotion operation, LTD4 acceptor antagonism, an elimination operation of reactive oxygen species, etc. The compound [I] of division and this invention tends to show notably peroxylipid generation reaction depressant action (antioxidation operation) among these aforementioned operations.

[0028] Moreover, the toxicity of a compound [I] and a side effect are low. therefore, the compound [I] of this invention — mammalian (a mouse, a rat, and a rabbit —) The thrombosis by the platelet aggregation in a dog, an ape, Homo sapiens, etc., an alignment, lungs, The ischemic disease by contraction or vasospasm of a brain and the arterial blood tubing smooth muscle in a kidney for example, (myocardial infarction and cerebral apoplexy), and a neurodegenerative disease (an example and Parkinson's disease —) An Alzheimer disease, a roux GERIHHI Mr. disease, myotrophia dystonica, a craniocerebral trauma, the functional disorder and memory disorder accompanying central damages, such as a spine trauma, and the emotional disorder (an oxygen deficiency —) The failure accompanying the nerve cell necrosis caused by brain injury, cerebral apoplexy, cerebral infarction, cerebral thrombosis, etc., The spasm and epilepsy which happen after cerebral apoplexy, cerebral infarction, and brain surgery and a craniocerebral trauma, A nephritis, pulmonmry insufficiency, bronchial asthma, inflammation, arteriosclerosis, atheromatous-degeneration arteriosclerosis, hepatitis, acute hepatitis, liver cirrhosis, anaphylaxis hepatitis, an immunodeficiency disease, and reactive oxygen species (super oxide —) the circulatory system disease (myocardial infarction —) caused by failures, such as an enzyme by a hydroxylation radical etc., a body tissue, and a cell Cerebral apoplexy, the cerebral edema, a nephritis, etc. have a therapy and a preventive effect to many diseases, such as an organization fibrosis phenomenon and oncogenesis. For example, it is useful as physic, such as a vantithrombotic, an anti-vasospasm agent, an anti-asthmatic agent, an antiallergic agent, an alignment, a cerebral circulatory system improvement agent, a nephritis therapy agent, a hepatitis therapy agent, an organization fibrosis inhibition agent, a reactive-oxygen-species elimination agent, and an arachidonate cascade matter accommodation improvement agent.

[0029] a compound [I] — remaining as it is or the very thing — insurance can be medicated taking-orally-wise as a physic constituent (an example, a tablet, a capsule, liquids and solutions, injections, suppositories) mixed with the well-known support permitted pharmacologically, an excipient, etc., or parenterally. Although a dose changes with the administration root for administration, symptoms, etc., when administering orally to the patient of of an adult circulatory system disease for example, it is usually convenient about 0.1 mg/kg - 20 mg/kg weight extent, and to prescribe 0.2 mg/kg - 10 mg/kg weight extent for the patient about 1 to 3 times per day preferably as an amount once.

[0030]

[Example] Although an example, the example of reference, and the example of a trial are given and this invention is explained in more detail below, this invention is not limited to these. example 15-amino-2-benzyl -2, 4 and 6, 7-tetramethyl-2, and 3-dihydrobenzofuran 4-amino - a sulfuric acid (15ml) is added to the dichloromethane (100ml) solution of a 2, 3, and 5-trimethyl phenol (20.0g, 0.13 mols) and 2-methyl-3-phenyl-2-propenol (25.0g, 0.17 mols) — heating reflux was carried out for 1 hour. Saturation sodium-hydrogencarbonate water neutralizes reaction mixture, Ethyl acetate extracted the product. An extract is rinsing, After desiccation, The solvent was distilled off. A silica gel column chromatography (isopropyl ether) refines residue, It was made to crystallize from a hexane and 7.2g (yield 19.3%) of specified substance was obtained. Melting point 68 to 69 degree C. NMR (CDCl3) delta 1.38 (3H, s), 2.06 (3H, s), 2.10 (3H, s), 2.16 (3H, s), 2.80 (2H, broads), 2.85 (2H, d, J= 13.6Hz), 3.08 (2H, d, J= 13.6Hz), 7.26 (5H, m).

[0031] Example 25-amino [Heating reflux was carried out with the sulfuric acid (2ml) for 18 hours.] - 2, 2, 4, 6, 7-pentamethyl -2, 3-dihydrobenzofuran hydrochloride 4-amino - It is in dichloromethane (20ml) about a 2, 3, and 5-trimethyl phenol (2.0g, 13.2mmol) and 2-methyl-2-propenol (1.15g, 15.8mmol), Saturation sodium-hydrogencarbonate water washes reaction mixture, It condensed after desiccation. A silica gel column chromatography (isopropyl ether) refines residue, After making it a hydrochloride, it was made to crystallize from ethanol-isopropyl ether and 460mg (yield 14.4%) of specified substance was obtained. Melting point 248 to 250 degree C (decomp). NMR (DMSO-d6) delta 1.47 (6H, s), 2.08 (3H, s), 2.18 (6H, s), 3.03 (2H, s), 9.80 (2H, broad s).

[0032] Example 35-amino - 2, 2, 4, 6, 7-pentamethyl -2, 3-dihydrobenzofuran hydrochloride 4-formylamino - 2, 3, and 5-trimethyl-1-(2-methyl-2-propenyloxy) benzene (7.33g, 35.7mmol) was dissolved in the methanol (100ml), and concentrated hydrochloric acid (30ml) was added to this under ice-cooling. After the argon permuted the inside of a flask, heating reflux was carried out for 2 hours. The chloroform extraction of the reaction mixture was neutralized and carried out with the sodium bicarbonate water after cooling. After [washing] vacuum concentration of the extract was rinsed and carried out, residue was crystallized from isopropyl ether, and 6.40g (yield 99.2%) was obtained. It recrystallized [methanol], after making a part into a hydrochloride. Melting point 248 to 250 degree C (decomposition). NMR (DMSO-d6) delta 1.41 (6H, s), 2.02 (3H, s), 2.20 (6H, s), 2.96 (2H, s), 9.65 (2H, broad s).

[0033] Example 45-amino - It compounded according to the approach of the 2, 2, 4, 6-tetramethyl-7-(2-methyl-1-propenyl)-2, and 3-dihydrobenzofuran hydrochloride above. Yield 80.1%. The 207 to 208 degree C (ethanol) melting point.
NMR (DMSO-d6) delta 1.39 (6H, s), 1.46 (3H, s), 1.86 (3H, s), 2.13 (3H, s), 2.21 (3H, s), 2.97 (2H, s), 5.90 (1H, s), 9.38 (2H, broad s).

[0034] Example 55-acetylamino [It compounded according to the approach of 48.] - 2, 2, 6, 7-tetramethyl-4-nitro -2, example of 3-dihydrobenzofuran reference Yield 89.4%. The melting point of 203 degrees C (dichloromethane-isopropyl ether).
NMR (CDCl3) delta 1.48 (6H, s), 2.15 (3H, s), 2.18 (3H, s), 2.19 (3H, s), 3.29 (2H, s), 7.79 (1H, broad s).

[0035] Example 65-acetylamino - 2, 2, 4, 7-tetramethyl-6-nitro -It compounded according to the approach of the 2 and 3-dihydrobenzofuran above. Yield 77.6%. Melting point 203 to 204 degree C (dichloromethane-isopropyl ether).
NMR (CDCl3) delta 1.50 (6H, s), 2.09 (3H, s), 2.12 (3H, s), 2.14 (3H, s), 3.00 (2H, s), 7.09 (1H, s).

[0036] example 77-amino -2, 2, 4 and 5, 6-pentamethyl -2, 3-dihydrobenzofuran hydrochlorides 2, 2, 4, and 5, 6-pentamethyl-7-nitro-2, and 3-dihydrobenzofuran (310mg, 1.3mmol) is melted to ethanol (10ml) -- 5% The catalytic-reduction reaction was performed by making palladium carbon (0.6g) into a catalyst. It is the **** back about a catalyst, A filtrate is condensed, A silica gel column chromatography (hexane-isopropyl ether and 7:3) refines residue, and after making it a hydrochloride, it is made to crystallize from ethanol-isopropyl ether. 170mg (yield 53.5%) of specified substance was obtained. Melting point 207 to 212 degree C. NMR (DMSO-d6) delta 1.47 (6H, s), 2.08 (3H, s), 2.12 (3H, s), 2.18 (3H, s), 3.03 (2H, s), 9.80 (2H, broad s).

[0037] example the 85-amino -2, 2, 4 and 6, the 7-pentamethyl-3-phenyl -2, the 3-dihydrobenzofurans 2, 2, 4, and 6, the 7-pentamethyl-5-nitro-3-phenyl -2, and 3-dihydrobenzofuran (2.0g, 6.4mmol) are melted to ethanol (15ml) -- 5% The catalytic-reduction reaction was performed by making palladium carbon (2.0g) into a catalyst. It is the **** back about a catalyst, A filtrate is condensed, Residue was continuously refined and crystallized from the hexane with the silica gel column chromatography (isopropyl ether), and 1.33g (yield 73.6%) of specified substance was obtained. The 131 to 132 degree C melting point. NMR (CDCl3) delta 1.00 (3H, s), 1.48 (3H, s), 1.77 (3H, s), 2.12 (3H, s), 2.19 (3H, s), 3.10 (2H, broad s), 4.11 (1H, s), 6.95 (2H, m), 7.20 (3H, m).

[0038] Example It compounded according to 95-amino-3-(4-fluoro phenyl)-2, 2, 4 and 6, 7-pentamethyl -2, and the approach of the 3-dihydrobenzofuran above. Yield 70.2%. Melting point 126 to 127 degree C (hexane). NMR (CDCl3) delta 0.99 (3H, s), 1.47 (3H, s), 1.77 (3H, s), 2.12 (3H, s), 2.18 (3H, s), 3.10 (2H, broad s), 4.09 (1H, s) 6.93 (4H, m).

[0039] Example It compounded according to 105-amino-3-(4-isopropyl phenyl)-2, 2, 4 and 6, 7-pentamethyl -2, and the approach of the 3-dihydrobenzofuran above. Yield 85.0%. Melting point 134 to 135 degree C (hexane). NMR (CDCl3) delta 1.00 (3H, s) 1.22 (6H, d, J= 6.8Hz), 1.47 (3H, s), 1.78 (3H, s), 2.13 (3H, s), 2.19 (3H, s), 2.85 (1H, septet, J= 6.8Hz), 3.10 (2H, broad s), 4.08 (1H, s), 6.85 (2H, m), 7.07 (2H, d, J= 8.0Hz).
[0040] Example 115-amino - It compounded according to the approach of the 2, 2, 4, 6, 7-pentamethyl-3-(3-pyridyl)-2, and 3-dihydrobenzofuran above. Yield 53.8%. The 130 to 131 degree C (hexane) melting point. NMR (CDCl3) delta 1.02 (3H, s), 1.50 (3H, s), 1.77 (3H, s), 2.12 (3H, s), 2.19 (3H, s), 3.04 (2H, broad s), 4.12 (1H, s), 7.16 (2H, m), 8.36 (1H, m) 8.46 (1H, t, J= 3.2Hz).
[0041] Example It compounded according to 125-amino-3-(3-amino-4-dimethylamino phenyl)-2, 2, 4 and 6, 7-pentamethyl -2, and the approach of the 3-dihydrobenzofuran dihydrochloride above. Yield 42.4%. Amorphous. NMR (DMSO-d6) delta 1.04 (3H, s), 1.44 (3H, s), 1.99 (3H, s), 2.13 (3H, s), 2.29 (3H, s), 3.02 (6H, s), 4.24 (1H, s), and 6.00- 7.50 (5H, m) and 9.85 (2H, broad s).
[0042] Example 135-amino-3-isopropyl - It compounded according to 2, 2, 4, 6, 7-pentamethyl - 2, and the approach of the 3-dihydrobenzofuran hydrochloride above. Yield 76.6%. Melting point 225 to 230 degree C (ethanol). NMR (DMSO-d6) delta 0.70 (3H, d, J= 6.6Hz), 0.96 (3H, d, J= 6.6Hz), 1.21 (3H, s), 1.57 (3H, s), 1.62 (1H, m), 2.09 (3H, s), 2.53 (3H, s), 2.57 (3H, s), 2.76 (1H, d, J= 2.8Hz), 10.07 (2H, broad s).
[0043] Example 144, 5-diamino - 2, 2, 6, 7-tetramethyl - It compounded according to the approach of the 2 and 3-dihydrobenzofuran hydrochloride above. Yield 96.9%. Melting point 248 to 251 degree C (ethanol).
NMR (DMSO-d6) delta 1.39 (6H, s), 1.93 (3H, s), 2.09 (3H, s), 2.82 (2H, s), 3.36 (4H, broad s).
[0044] Example 155-acetylamino-6-amino - 2, 2, 4, 7-tetramethyl - It compounded according to the approach of the 2 and 3-dihydrobenzofuran above. Yield 98.7%. Melting point: 155 to 157 degree C (isopropyl ether).
NMR (CDCl3) 1.44 (6H, s), 1.82 and 2.23 (3H, s), 2.00-2.05 (6H, m), 2.87 (2H, s) and 3.75 (2H, broad s), and 6.40 and 6.62 (1H, broad s) (.) delta
[0045] Example 165-acetylamino-4-amino - 2, 2, 6, 7-tetramethyl - It compounded according to the approach of the 2 and 3-dihydrobenzofuran above. 91.4%. Melting point 172 to 173 degree C (ethanol-ether).
NMR (CDCl3) delta 1.46 (6H, s), 1.83 and 2.23 (3H, s), and 2.05- 2.09 (6H, m) and 2.83 (2H, s).
[0046] Example 175-amino - 2, 2, 4, 6, 7-pentamethyl-3-(4-methylphenyl)-2, the 3-dihydrobenzofurans 2, 2, 4, and 6, 7-pentamethyl-3-(4-methylphenyl)-5-nitro -2, 3-dihydrobenzofuran (1.26g) 3.9mmol(s) are melted to a methanol (30ml), Zinc dust (1.3g) and 1N-sodium hydroxide (15ml) were added, and heating reflux was carried out for 3 hours. Insoluble matter is ****(ed), Water was added and ethyl acetate extracted. Extract, After rinsing desiccation, The solvent was distilled off. A silica gel column chromatography (hexane-isopropyl ether and 95:5) refines residue, It is made to crystallize from a hexane and is the specified substance. 710mg (yield 53.7%) was obtained. Melting point 119 to 120 degree C. NMR (CDCl3) delta 1.00 (3H, s), 1.47 (3H, s), 1.78 (3H, s), 2.13 (3H, s), 2.20 (3H, s), 2.31 (3H, s), 3.20 (2H, broad s), 4.09 (1H, s), 6.82 (2H, m), 7.10 (2H, m).
[0047] Example 185-amino - It compounded according to the approach of the 2, 2, 4, 6, 7-pentamethyl-3-(4-propyl phenyl)-2, and 3-dihydrobenzofuran above. Yield 65.6%. Melting point 68 to 69 degree C (methanol). NMR (CDCl3) delta 0.90 (3H, t, J= 7.2Hz), 0.99 (3H, s), 1.47 (3H, s), 1.60 (2H, sextet, J= 7.2Hz), 1.77 (3H, s), 2.12 (3H, s), 2.19 (3H, s), 2.54 (2H, t, J= 7.2Hz), 3.10 (2H, broad s), 4.09 (1H, s), 6.82 (2H, m), 7.03 (2H, d, J= 8.0Hz).
[0048] Example 195-amino - It compounded according to the approach of the 2, 2, 4, 6, 7-pentamethyl-3-(4-pentyl phenyl)-2, and 3-dihydrobenzofuran above. Yield 55.6%. Melting point 67 to 68 degree C (methanol). NMR (CDCl3) delta 0.87 (3H, t, J= 6.6Hz), 1.00 (3H, s), 1.31 (4H, m), 1.47 (3H, s), 1.58 (2H, m), 1.78 (3H, s), 2.12 (3H, s), 2.19 (3H, s), 2.55 (2H, t, J= 7.2Hz), 3.20 (2H, broads), 4.09 (1H, s), 6.82 (2H, m), 7.03 (2H, d, J= 8.0Hz).
[0049] Example 205-amino - It compounded according to 2, 4, 6, 7-tetramethyl-2-piperidinomethyl -2, and the approach of the 3-dihydrobenzofuran above. Yield 82.1%. Melting

point 60 to 61 degree C (isopropyl ether). NMR (CDCl3) delta 1.30-1.60 (6H, m), 1.42 (3H, s), 2.07 (6H, s) and 2.10 (3H, s), 2.35-2.65 (6H, m), 2.80 (1H, d, J= 15.9Hz), 3.10 (2H, broad s), 3.11 (1H, d, J= 15.9Hz).

[0050] Example 215-amino - It compounded according to 2, 4, 6, the 7-tetramethyl-2-morpholino methyl -2, and the approach of the 3-dihydrobenzofuran above. Yield 38.0%. Melting point 114 to 115 degree C (isopropyl ether).

NMR (CDCl3) delta 1.42 (3H, s), 2.07 (9H, s), 2.40-2.70 (6H, m), 2.81 (1H, d, J= 15.0Hz), 3.13 (1H, d, J= 15.0Hz), 3.20 (2H, broad s), 3.67 (4H, t, J= 4.6Hz).

[0051] Example 225-amino - It compounded according to the approach of the 2, 4, 6, 7-tetramethyl-2-[2-(dimethylamino) ethyl]-2, and 3-dihydrobenzofuran dihydrochloride above. Yield 46.5%. Melting point 200 to 203 degree C (decomposition) (ethanol-isopropyl ether). NMR (DMSO-d6) delta 1.41 (3H, s) 2.06 (3H, s), 2.17 (2H, m), 2.22 (3H, s), 2.24 (3H, s), 2.74 (6H, s), 2.96 (1H, d, J= 16.0Hz), 3.11 (2H, m), 3.16 (1H, d, J= 16.0Hz), 9.78 (2H, broad s).

[0052] Example 235-amino - It compounded according to the approach of the 2, 4, 6, 7-tetramethyl-2-(2-piperidino ethyl)-2, and 3-dihydrobenzofuran dihydrochloride above. Yield 41.9%. Melting point 260 to 270 degree C (decomposition) (ethanol-isopropyl ether). NMR (DMSO-d6) delta 1.41 (3H, s) 1.76 (6H, m), 2.06 (3H, s), 2.22 (3H, s), 2.23 (3H, s), 2.23 (2H, m), 2.84 (4H, m), 2.95 (1H, d, J= 15.8Hz), 3.05 (2H, m), 3.15 (1H, d, J= 15.8Hz), 9.65 (2H, broad s).

[0053] Example 245-amino - The dimethylamine water solution (6.46ml, 64.2mmol) was dropped at the ethanol (10ml) suspension of 2, 2, 4, the 6-tetramethyl-7-(dimethylamino) methyl -2, and a 3-dihydrobenzofuran oxalate paraformaldehyde (1.61g, 42.8mmol) 50%, and this mixture was agitated until it became homogeneity at the room temperature (for 30 minutes). This solution was dropped at the ethanol (30ml) solution of 4-acetylamino -3 and a 5-dimethyl-2-(2-methyl-2-propenyl) phenol (4.98g, 21.4mmol), and the heating reflux of the mixture was carried out under the argon ambient atmosphere for 3.5 hours. It condensed under reduced pressure after cooling reaction mixture. The silica gel column chromatography (a chloroform-methanol, 95:5) refined the residue, and 5.45g (yield 87.7%) of specified substance was obtained as brown oily matter. This was dissolved in the methanol (60ml), concentrated hydrochloric acid (20ml) was added, and the heating reflux of this mixture was carried out under the argon ambient atmosphere for 1.5 hours. The chloroform extraction of the superfluous sodium bicarbonate water was added and carried out after cooling reaction mixture. The extract was condensed after rinsing and desiccation. The silica gel column chromatography (a chloroform-methanol, 88:12) refined residue, and 4.86g (yield 90.5%) of specified substance was obtained as brown oily matter. This was dissolved in ethanol (3ml), 5-N sodium hydroxide (25ml) was added, and mixture was agitated at 200 degrees C the bottom of an argon ambient atmosphere, and among the sealed tube for 13 hours. The water after cooling was added and the chloroform extraction of the reaction mixture was carried out. The extract was condensed after rinsing and desiccation. The silica gel column chromatography (a chloroform-methanol, 88:12) refined residue, and 1.70g (yield 41.5%) was obtained. It recrystallized [ethanol] and the specified substance was obtained, after making this part into an oxalate. Melting point: 178 to 180 degree C (ethanol).

NMR delta (DMSO-d6) 1.39 (6H, s), 2.02 (3H, s), 2.07 (3H, s), 2.74 (6H, s), 2.93 (2H, s), 4.13 (2H, s), 4.52 (4H, broad s).

[0054] Example 255-amino - It compounded according to 2, 2, 4, 6-tetramethyl-7-piperidinomethyl -2, and the approach of the 3-dihydrobenzofuran oxalate above. Yield 47.9%-41.0%-55.7%. Melting point 110 to 112 degree C (ethanol).

NMR delta(DMSO-d6): 1.44 (6H, s), 1.62-1.80 (6H, m), 2.01 (3H, s), 2.03 (3H, s), 2.99 (2H, s), 3.11 (4H, broad s), 4.09 (2H, s), 4.48 (4H, broad s).

[0055] Example 265-amino - It compounded according to 2, 2, 4, the 6-tetramethyl-7-morpholino methyl -2, and the approach of the 3-dihydrobenzofuran oxalate above. Yield 55.1%-77.3%-55.2%. Melting point 118 to 120 degree C (ethanol).

NMR delta (DMSO-d6) 1.38 (6H, s), 2.01 (3H, s), 2.08 (3H, s), 2.85 (4H, broad s), 2.90 (2H, s), 3.68 (4H, broad s), 3.83 (2H, s), 5.03 (4H, broad s).

[0056] Example 275-acetylamino-2-hydroxymethyl [- A 2, 3, and 5-trimethyl-6-(2-MECHIRU 2-propenyl) phenol (2.0g, 8.1mmol) is melted to dichloromethane (20ml), / m-chloro perbenzoic

acid (70% of purity, 2.2g, 8.9mmol) was added little by little with the bottom scrambling of ice-cooling.] - 2, 4, 6, 7-tetramethyl - 2, 3-dihydrobenzofuran 4-acetylamino After addition termination, Reaction mixture is stirred at a room temperature for 1 hour, Triethylamine (2ml) was added. Reaction mixture is rinsed, It condensed after desiccation. The silica gel column chromatography (ethyl acetate) refined residue, and 1.1g (yield 51.7%) of specified substance was obtained. Oily. NMR (CDCl3) delta 1.43 (3H, s), 1.96 (1H, m), 2.07 (3H, s), 2.09 (6H, s), 2.20 (3H, s), 2.81 (1H, d, J= 15.4Hz), 3.16 (1H, d, J= 15.4Hz), 3.63 (2H, m), 6.66 (1H, broad s).

[0057] Example 285-formylamino-2-hydroxymethyl - 2, 4, 6, 7-tetramethyl - It compounded according to the approach of the 2 and 3-dihydrobenzofuran above. Yield 59.9%. Melting point 149 to 150 degree C (ethyl-acetate-hexane). NMR (DMSO-d6) delta 1.33 (3H, s) 1.97 (3H, s), 1.98 (3H, s), 2.00 (3H, s), 2.73 (1H, d, J= 15.4Hz), 3.13 (1H, d, J= 15.4Hz) 3.42 (2H, d, J= 5.8Hz), 5.01 (1H, t, J= 5.8Hz), 7.83 (0.2H, d, J= 11.6Hz), 8.21 (0.8H, d, J=1.2H), 9.05 (0.2H, d, J= 11.6Hz), 9.20 (0.8H, broad s).

[0058] Example 292-bromomethyl-5-formylamino [- A 2, 3, and 5-trimethyl-6-(2-MECHIRU 2-propenyl) phenol (50g, 0.21 mols) and sodium acetate (30.5g, 0.37 mols) were put in into the acetic acid (500ml), and the bromine (16 or 5ml, 0.21 mols) was dropped with scrambling.] - 2, 4, 6, 7-tetramethyl - 2, 3-dihydrobenzofuran 4-formylamino After stirring reaction mixture for 30 minutes It pours into iced water, Ethyl acetate extracted the product., Saturation sodium-hydrogencarbonate water washes an extract, It condensed after desiccation. Residue is remelted to ethyl acetate, Insoluble matter was ****(ed). A filtrate is condensed, The crystal which added isopropyl ether and deposited is ****(ed), 44.0g (yield 65.7%) of specified substance was obtained. Melting point 157 to 158 degree C. NMR (CDCl3) delta 1.61 (1.5H, s) 1.63 (1.5H, s), 2.09 (3H, s), 2.11 (3H, s), 2.13 (1.5H, s), 2.16 (1.5H, s) 2.93 (1H, d, J= 15.8Hz), 3.28 (0.5H, d, J= 15.8Hz) 3.29 (0.5H, d, J= 15.8Hz), 3.51 (1H, s), 3.53 (1H, s), 6.77 (0.5H, broad s), 6.85 (0.5H, d, J= 12.0Hz), 7.96 (0.5H, d, J= 12.0Hz), 8.40 (0.5H, d, J= 1.4Hz).

[0059] Example 305-acetylamino-2-formyl [Dimethyl sulfoxide (1ml) was dropped with scrambling.] - 2, 4, 6, 7-tetramethyl - The dichloromethane (10ml) solution of a 2 and 3-dihydrobenzofuran oxalyl chloride (0.45ml, 4.7mmol) is cooled at -78 degrees C, 5-acetylamino-2-hydroxymethyl after stirring at this temperature for 2 hours - 2, 4, 6, 7-tetramethyl - The dichloromethane (5ml) solution of 2 and 3-dihydrobenzofuran (1.1g, 4.2mmol) is dropped, It stirred for 30 more minutes. triethylamine (3.5ml) is added -- after stirring for 10 minutes, 1N-hydrochloric acid and saturation sodium-hydrogencarbonate water washed reaction mixture. It condenses after drying reaction mixture, A silica gel column chromatography (ethyl acetate) refines residue, 0.47g (yield 43.1%) of specified substance was obtained. Oily. NMR (CDCl3) delta 1.55 (3H, s), 2.06 (3H, s), 2.11 (3H, s), 2.13 (3H, s), 2.21 (3H, s), 2.94 (1H, d, J= 15.8Hz), 3.41 (1H, d, J= 15.8Hz), 6.72 (1H, broad s).

[0060] Example 312-formyl-5-formylamino - 2, 4, 6, 7-tetramethyl - It compounded according to the approach of the 2 and 3-dihydrobenzofuran above. Yield 25.5%. Oily. NMR (CDCl3) delta 1.55 (1.5H, s) 1.57 (1.5H, s), 2.08 (3H, s), 2.12 (3H, s), 2.15 (3H, s), 2.94 (1H, d, J= 15.4Hz) 3.41 (0.5H, d, J= 15.4Hz), 3.44 (0.5H, d, J= 15.4Hz), 7.00 (1H, m), 7.95 (0.5H, d, J= 12.0Hz), 8.34 (0.5H, d, J= 1.8Hz), 9.73 (0.5H, s), 9.74 (0.5H, s).

[0061] example the tetrahydrofuran (10ml) suspension of 32(Z)-5-acetylamino -2, 4 and 6, the 7-tetramethyl-2-styryl -2, and 3-dihydrobenzofuran benzyltriphenylphosphonium chloride (0.7g, 1.8mmol) is cooled at -20 degrees C -- n-butyl lithium hexane solution (1.6M, 1.12 ml, 1.8mmol) was dropped. 5-acetylamino-2-formyl after stirring reaction mixture for 30 minutes - 2, 4, 6, 7-tetramethyl - The tetrahydrofuran (5ml) solution of 2, 3, and - dihydrobenzofuran (0.45g, 1.7mmol) is dropped, It stirred at the room temperature for 30 more minutes. Water is added to reaction mixture, Ethyl acetate extracts a product, It is rinsing about an extract, It condensed after desiccation. A silica gel column chromatography (isopropyl ether-ethyl acetate and 1:1) refines residue, 0.44g (yield 76.2%) of specified substance was obtained. Oily. NMR (CDCl3) delta 1.55 (3H, s) 1.87 (3H, s), 1.98 (3H, s), 2.05 (3H, s), 2.19 (3H, s), 2.94 (1H, d, J= 15.4Hz), 3.19 (1H, d, J= 15.4Hz), 5.92 (1H, d, J= 12.8Hz), 6.50 (1H, d, J= 12.8Hz), 6.62 (1H, broad s), 7.25 (5H, m).

[0062] Example 33(Z)-5-acetylamino - It compounded according to the approach of the 2, 4, 6, 7-tetramethyl-2-[2-(4-fluoro phenyl) ethenyl]-2, and 3-dihydrobenzofuran above. Yield 81.3%

(oily). NMR (CDCl3) delta 1.55 (3H, s) 1.84 (3H, s), 2.00 (3H, s), 2.05 (3H, s), 2.19 (3H, s), 2.95 (1H, d, J= 14.0Hz), 3.19 (1H, d, J= 14.0Hz), 5.88 (1H, d, J= 12.6Hz), 6.45 (1H, d, J= 12.6Hz), 6.69 (1H, broad s), 7.00 (2H, m), 7.26 (2H, m).

[0063] Example 3-[5-formylamino -2, 4 and 6, 7-tetramethyl-2, and 3-dihydrobenzofuran-2-IRU] acrylate 2-formyl-5-formylamino - 2, 4, 6, 7-tetramethyl 34 ethyl - 2, 3, - dihydrobenzofuran (1.0g) 4.1mmol(s), Triethyl phosphono acetate (0.91g, 4.1mmol), And sodium hydride (60% of purity, 162 mg, 4.1mmol) was added into dimethylformamide, and was stirred at the room temperature for 1 hour. Reaction mixture is diluted with water, Ethyl acetate extracted the product. An extract is rinsing, After desiccation, The solvent was distilled off. A silica gel column chromatography (ethyl-acetate-isopropyl ether and 1:1) refines residue, 0.5g (39.0% of yield) of specified substance was obtained. Oily. NMR (CDCl3) delta 1.29 (3H, t, J= 7.2Hz), 1.60 (3H, s), 2.06 (1.5H, s), 2.11 (1.5H, s), 2.13 (1.5H, s), 2.15 (1.5H, s), 2.17 (3H, s), 3.05 (1H, d, J= 15.4Hz) 3.15 (1H, d, J= 15.4Hz), 4.19 (2H, d, J= 7.2Hz) 6.02 (1H, d, J= 15.6Hz), 6.92 (0.5H, broad s), 6.95 (0.5H, d, J= 12.0Hz), 7.02 (1H, d, J= 15.6Hz), 7.95 (0.5H, d, J= 12.0Hz), 8.39 (0.5H, d, J= 1.6Hz).

[0064] Example 355-acetylamino [5% Palladium carbon (0.3g) was added and it stirred under the hydrogen ambient atmosphere for 1 hour.] - 2, 4, 6, 7-tetramethyl-2-(2-phenylethyl)-2, 3-dihydro(benzofuran Z)-5-acetylamino - In 2, 4, 6, the 7-tetramethyl-2-styryl -2, and the ethanol solution of 3-dihydrobenzofuran (1.0g, 3.0mmol) **** back liquid was condensed for the catalyst, the silica gel column chromatography (isopropyl ether-ethyl acetate and 1:1) refined residue, and 0.95g (yield 94.4%) of specified substance was obtained. Oily.

NMR (CDCl3) delta 1.48 (3H, s) 2.02 (2H, m), 2.05 (3H, s), 2.09 (3H, s), 2.14 (3H, s), 2.22 (3H, s) and 2.72 (2H, m) -- 2.89 (1H, d, J= 15.4Hz), 3.05 (1H, d, J= 15.4Hz), and 7.10- 7.30 (5H, m) and 7.15 (1H, broad s).

[0065] Example 365-acetylamino-2-[2-(4-fluoro phenyl) ethyl]-2, 4 and 6, 7-tetramethyl - It compounded according to the approach of the 2 and 3-dihydrobenzofuran above. Yield 90.3%. Oily. NMR (CDCl3) delta 1.47 (3H, s) 1.98 (2H, m), 2.06 (3H, s), 2.10 (6H, s), 2.20 (3H, s), 2.69 (2H, m), 2.90 (1H, d, J= 15.4Hz), 3.05 (1H, d, J= 15.4Hz), 6.70 (1H, broad s), 6.95 (2H, m), 7.13 (2H, m).

[0066] Example 375-amino-7-(2-methylpropyl)-2, 2 and 4, 6-tetramethyl - 2, 3-dihydrobenzofuran hydrochloride 5-amino-7-(2-methyl-1-propenyl)-2, 2 and 4, 6-tetramethyl - 2, 3-dihydrobenzofuran (1.50g) Palladium carbon (1.0g) was added to the ethanol (100ml) solution of 6.11mmol(s) 10%, and heating reflux was carried out under the hydrogen ambient atmosphere for 3 hours. It filtered and the filtrate was condensed, after cooling reaction mixture. Residue was crystallized from isopropyl ether and 1.45g (yield 95.9%) was obtained. After making this into a hydrochloride by HCl/EtOH, it recrystallizes [ethanol], and it is the specified substance. 0.90g (51.9%) was obtained. Melting point: 223 to 225 degree C (ethanol).

NMR delta (DMSO-d6) 0.85 (6H, d, J= 6.6Hz), 1.39 (6H, s), 1.63-1.84 (1H, m), 2.21 (3H, s), 2.22 (3H, s), 2.38 (2H, d, J= 7.2Hz), 2.96 (2H, s), 9.54 (2H, broad s).

[0067] example 385-formylamino -2, 2, 4 and 6, 7-pentamethyl -2, the 3-dihydrobenzofuran 5-amino -2, 2, 4 and 6, 7-pentamethyl -2, and 3-dihydrobenzofuran (1.00g, 4.87mmol) are melted to a formic acid (20ml) -- heating reflux was carried out for 48 hours. After condensing reaction mixture under reduced pressure and adding saturation sodium bicarbonate water to residue, the chloroform extraction of this was carried out. With saturation brine, after washing, it dried and the extract was condensed under reduced pressure. The silica gel column chromatography (a chloroform-methanol, 97:3) refined residue, and 1.06g (yield 93.3%) of specified substance was obtained. A part is ******ed from dichloromethane-isopropyl ether and it is the melting point. White prism ** of 177 to 179 degree C was obtained.

NMR (CDCl3) delta 1.46 (3H, s), 1.48 (3H, s), 2.09-2.16 (9H, m), 2.94 (2H, s), 6.68 (1H, broad s), 7.97 (0.5H, d, J= 12.0Hz), 8.40 (0.5H, d, J= 1.4Hz).

[0068] Example 395-acetylamino - 2, 2, 4, 6, 7-pentamethyl -2, 3-dihydrobenzofuran 5-amino - In 2, 2, 4, 6, 7-pentamethyl -2, 3-dihydrobenzofuran (1.00g, 4.87mmol), and the tetrahydrofuran (20ml) solution of triethylamine (640mg, 6.33mmol), acetyl chloride (460mg, 5.84mmol) was dropped under ice-cooling, and was agitated after dropping termination for 4 hours. The chloroform extraction of the water was added and carried out to reaction mixture. With saturation sodium bicarbonate water and saturation brine, it dried after washing and the extract

was condensed. The silica gel column chromatography (a chloroform-methanol, 97:3) refined the residue, and 920mg (yield 76.4%) of specified substance was obtained. The part was ******ed from dichloromethane-isopropyl ether. Melting point: 190 degrees C (dichloromethane-isopropyl ether).
NMR delta (CDCl3) 1.46 (6H, s), 1.73 and 2.21 (3H, s), 2.06 (3H, s), 2.09 (3H, s), 2.14 (3H, s), and 2.93 (2H, s), 6.63(1H, broad s). [0069] Example It compounded according to 402, 2, 4, 6, 7-pentamethyl-5-propionylamino -2, and the approach of the 3-dihydrobenzofuran above. Yield 99.8%. Melting point: 146 degrees C (dichloromethane-isopropyl ether).
NMR delta (CDCl3) 1.06 and 1.31 (3H, t, J= 7.4Hz), 1.46 and 1.50 (6H, s), 1.92 and 2.44 (2H, q, J= 7.4Hz), and 2.04- 2.13 (9H, m), 2.93 (2H, s), and 6.53 and 6.59 (1H, broad s).
[0070] Example 415-butyryl amino - It compounded according to 2, 2, 4, 6, 7-pentamethyl -2, and the approach of the 3-dihydrobenzofuran above. Yield 70.8%. Melting point 136 to 138 degree C (dichloromethane-isopropyl ether).
NMR delta (CDCl3) 0.87 and 1.05 (3H, t, J= 7.4Hz), 1.46 and 1.51 (6H, s), 1.74-1.92 (2H, m), 2.05-2.09 (9H, m), 2.10-2.12 (2H, m), 2.39 (2H, t, J= 7.4Hz) and 2.93 (2H, s), 6.52-6.62 (1H, m), and 6.53 and 6.60 (1H, broad s).
[0071] Example 425-benzoylamino - It compounded according to 2, 2, 4, 6, 7-pentamethyl -2, and the approach of the 3-dihydrobenzofuran above. Yield 84.5%. Melting point 263 to 265 degree C (dichloromethane-isopropyl ether).
NMR delta (CDCl3) 1.48 (6H, s), 2.12 (6H, s), 2.16 (3H, s), 2.96 (2H, s), 7.45-7.57 (3H, m), 7.90-7.96 (2H, m).
[0072] Example 435-isobutyryl amino - It compounded according to 2, 2, 4, 6, 7-pentamethyl -2, and the approach of the 3-dihydrobenzofuran above. Yield 92.3%. Melting point 170 to 172 degree C (dichloromethane-isopropyl ether).
NMR delta (CDCl3) 1.30 (6H, d, J= 7.0Hz), 1.46 (6H, s), 2.03 (3H, s), 2.08 (6H, s), 2.61 (1H, septet, J= 7.0Hz), 2.92 (2H, s), 6.57 (1H, broad s).
[0073] Example 445-ethoxycarbonylamino - It compounded according to 2, 2, 4, 6, 7-pentamethyl -2, and the approach of the 3-dihydrobenzofuran above. Yield 74.6%. Melting point 102 to 104 degree C (isopropyl ether-pentane).
NMR delta (CDCl3) 1.31 (3H, t, J= 7.4Hz), 1.45 and 1.46 (6H, s), 2.09 (6H, s), 2.13 (3H, s), 2.93 (2H, s), and 4.20 (2H, q, J= 7.4Hz), 5.87(1H, broad s). [0074] Example 455-methanesulfonylamino - It compounded according to 2, 2, 4, 6, 7-pentamethyl -2, and the approach of the 3-dihydrobenzofuran above. Yield 65.7%. Melting point 159 to 160 degree C (dichloromethane-isopropyl ether).
NMR delta (CDCl3) 1.47 (6H, s), 2.10 (3H, s), 2.25 (3H, s), 2.28 (3H, s), 2.93 (2H, s), 3.03 (3H, s), 5.70 (1H, s).
[0075] Example 462, 2, 4, 6, 7-pentamethyl-5-(p-toluenesulfonyl amino)-2, 3-dihydrobenzofuran 5-amino - 2, 2, 4, 6, 7-pentamethyl -2, 3-dihydrobenzofuran (2.00g, 9.74mmol), and p-tosyl chloride (2.04g, 10.7mmol) were dissolved in the pyridine (30ml), and it agitated at 50 degrees C for 1 hour. Reaction mixture was condensed under reduced pressure and residue was dissolved in chloroform. This was dried after washing with 1-N hydrochloric acid and saturation brine, and the solvent was distilled off under reduced pressure. The silica gel column chromatography (hexane-ethyl acetate, 97:3) refined ******, the rough crystal was ******ed from dichloromethane-isopropyl ether, and 2.41g (yield 68.8%) of specified substance was obtained. Melting point 219 to 220 degree C (dichloromethane-isopropyl ether).
NMR delta (CDCl3) 1.46 (6H, s), 1.80 (3H, s), 1.93 (3H, s), 2.01 (3H, s), 2.43 (3H, s), 2.87 (2H, s), 5.81 (1H, s), 7.24 (2H, d, J= 8.4Hz), 7.60(2H, d, J= 8.4Hz). [0076] example 475-ethylamino-2-[2-(4-fluoro phenyl) Ethyl] -2, 4 and 6, 7-tetramethyl - 2, 3-dihydrobenzofuran 5-acetylamino - 2, 4, 6, 7-tetramethyl-2-[2-(4-fluoro phenyl) ethyl]-2, 3-dihydrobenzofuran (1.2g) 3.4mmol(s) and lithium hydride aluminum are added into a tetrahydrofuran (20ml) -- heating reflux was carried out for 3 hours. Reaction mixture was poured out into iced water and extracted the product with ethyl acetate. An extract distills off the solvent after rinsing and desiccation, A silica gel column chromatography (isopropyl ether-ethyl acetate and 2:1) refines residue, 0.82g (yield 71.2%) of specified substance was obtained. Oily. NMR (CDCl3) delta 1.21 (3H, t, J= 7.2Hz), 1.47 (3H, s),

1.98 (2H, m), 2.11 (3H, s), 2.14 (3H, s), 2.19 (3H, s), 2.70 (2H, m), 2.84 (2H, q, J= 7.2Hz), 2.85 (1H, broad s), 2.90 (1H, d, J= 14.0Hz), 3.02 (1H, d, J= 14.0Hz), 6.94 (2H, m), 7.12 (2H, m).
[0077] Example 485-methylamino - 2, 2, 4, 6, 7-pentamethyl -2, 3-dihydrobenzofuran hydrochloride 5-amino - The lithium aluminum hydride (2.93g, 77.2mmol) was added to the tetrahydrofuran (150ml) solution of 2, 2, 4, 6, 7-pentamethyl -2, and 3-dihydrofuran (9.00g, 38.6mmol) under ice-cooling, and heating reflux was carried out under the argon ambient atmosphere for 5 hours. After cooling reaction mixture Water (4.8ml) was added and filtered. The filtrate was condensed under reduced pressure and the silica gel column chromatography (hexane-ethyl acetate, 9:1) refined residue, after making it a hydrochloride, it recrystallized [ether / ethanol-], and 4.03g (yield 40.8%) of specified substance was obtained. Melting point 205 to 208 degree C (ethanol-ether).
NMR delta (CDCl3) 1.46 (6H, s), 2.08 (3H, s), 2.48 (6H, s), 2.92 (2H, s), and 2.98- 3.02 (3H, m) and 10.57 (1H, broad s).
[0078] Example 495-ethylamino - It compounded according to 2, 2, 4, 6, 7-pentamethyl -2, and the approach of the 3-dihydrobenzofuran hydrochloride above. Yield 34.0%. Oily.
NMR delta (CDCl3) 1.45 (6H, s), 1.48 (3H, t, J= 8.4Hz), 2.07 (3H, s), 2.47 (3H, s), 2.48 (3H, s), 2.91 (2H, s), and 3.35- 3.48 (2H, m) and 10.53 (1H, broad s).
[0079] Example It compounded according to 502, 2, 4, 6, 7-pentamethyl-5-propylamino -2, and the approach of the 3-dihydrobenzofuran hydrochloride above. Yield 43.2%. Melting point 185 to 187 degree C (ethanol-ether).
NMR delta (CDCl3) 0.92 (3H, t, J= 7.4Hz), 1.45 (6H, s), 1.93-2.06 (2H, m), 2.07 (3H, s), 2.47 (3H, s), 2.48 (3H, s) and 2.91 (2H, s), and 3.15- 3.29 (2H, m) and 10.54 (1H, broad s).
[0080] Example 515-butylamino - It compounded according to 2, 2, 4, 6, 7-pentamethyl -2, and the approach of the 3-dihydrobenzofuran hydrochloride above. Yield 39.7%. Melting point 158 to 160 degree C (ethanol-ether).
NMR delta(CDCl3): 0.86 (3H, t, J= 7.4Hz), 1.23- 1.38 (2H, m), 1.45 (6H, s), and 1.91-2.06 (2H, m) - - 2.07 (3H, s), 2.47 (3H, s), 2.49 (3H, s), 2.91 (2H, s), and 3.17- 3.32 (2H, m) and 10.57 (1H, broad s).
[0081] Example 525-benzylamino - It compounded according to 2, 2, 4, 6, 7-pentamethyl -2, and the approach of the 3-dihydrobenzofuran hydrochloride above. Yield 32.3%. Melting point 155 to 157 degree C (ethanol-ether).
NMR delta (CDCl3) 1.44 (6H, s), 2.02 (3H, s), 2.10 (3H, m), 2.20 (3H, s), 2.82 (2H, s), 4.56 (2H, broad s), and 7.19- 7.32 (5H, m) and 10.89 (1H, broad s).
[0082] Example It compounded according to 532, 2, 4, 6, the 7-pentamethyl-5-(2-methylpropyl) amino -2, and the approach of the 3-dihydrobenzofuran hydrochloride above. Yield 67.1%. Oily.
NMR delta (CDCl3) 1.10 (6H, d, J= 6.6Hz), 1.45 (6H, s), 2.05 (3H, s), 2.44 (3H, s), 2.48 (3H, s), and 2.54- 2.80 (1H, m), 2.90 (2H, s), and 2.93- 3.04 (2H, m) and 10.39 (1H, broad s).
[0083] Example 545-acetylamino-4-dimethylamino [- 2, 2, 6, 7-tetramethyl / - Potassium carbonate (4.42g, 32.0mmol) and a methyl iodide (3.99ml 63.9mmol) were added to the dimethylformamide (100ml) solution of 2 and 3-dihydrobenzofuran (5.30g, 21.3mmol), and it agitated at the room temperature for 3 hours.] - 2, 2, 6, 7-tetramethyl - 2, 3-dihydrobenzofuran 5-acetylamino-4-amino Water was added to reaction mixture and ethyl acetate extracted this. The solvent was distilled off for the extract under reduced pressure after rinsing and desiccation. After the silica gel column chromatography (a chloroform-methanol, 97:3) refined residue, it recrystallized [isopropyl ether / dichloromethane-] and 5.52g (yield 93.6%) of specified substance was obtained. Melting point 186 degrees C. NMR delta (CDCl3) 1.44 (6H, s), 2.09 (6H, s), 2.21 (3H, s), 2.67 (6H, s), 3.09 (2H, s), 7.17 (1H, broads).
[0084] Example 555-acetylamino - It compounded according to 2, 2, 4, 7-tetramethyl-6-dimethylamino -2, and the approach of the 3-dihydrobenzofuran above. Yield 93.5%. Melting point 142 to 143 degree C (isopropyl ether).
NMR delta (CDCl3) 1.46 (6H, s), 2.04 (3H, s), 2.10 (3H, s), 2.20 (3H, s), 2.78 (6H, s), 2.90 (2H, s), 7.05 (1H, broad s).
[0085] Example 565-amino [- 50% dimethylamine water solution (20ml) is added to the methanol (20ml) solution of 2 and 3-dihydrobenzofuran (4.0g, 12.8mmol), / It heated at 160 degrees C

among the autoclave for 15 hours.] - 2, 4, 6, 7-tetramethyl-2-dimethyl aminomethyl -2, 3-dihydrobenzofuran 2-bromomethyl-5-formylamino - 2, 4, 6, 7-tetramethyl Reaction mixture is diluted with the water after cooling, Ethyl acetate extracted the product. An extract is the rinsing desiccation back, The solvent was distilled off. After the silica gel column chromatography (a chloroform-methanol and 95:5) refined residue, it recrystallized [isopropyl ether] and 2.9g (yield 91.2%) of specified substance was obtained. Melting point 66 to 67 degree C. NMR (CDCl3) delta 1.43 (3H, s), 2.07 (6H, s), 2.11 (3H, s), 2.33 (6H, s), 2.50 (2H, s), 2.82 (1H, d, J= 15.4Hz), 3.10 (2H, broad s), 3.12 (1H, d, J= 15.4Hz).

[0086] Example 575-amino [- To 2 and 3-dihydrobenzofuran (3.0g, 9.6mmol) / A pyrrolidine (20ml) is added, It heated at 160 degrees C among the autoclave for 15 hours.] - 2, 4, 6, the 7-tetramethyl-2-pyrrolidino methyl -2, 3-dihydrobenzofuran 2-bromomethyl-5-formylamino - 2, 4, 6, 7-tetramethyl Reaction mixture is diluted with the water after cooling, Ethyl acetate extracted the product. An extract is the rinsing desiccation back, The solvent was distilled off. A silica gel column chromatography (a chloroform-methanol and 9:1) refines residue, It recrystallized [hexane] and 2.2g (yield 83.5%) of specified substance was obtained. Melting point 85 to 86 degree C (decomposition). NMR (CDCl3) delta 1.44 (3H, s), 1.72 (4H, m), 2.06 (6H, s), 2.10 (3H, s), 2.45-2.65 (4H, m), 2.68 (2H, s), 2.81 (1H, d, J= 15.4Hz), 3.16 (1H, d, J= 15.4Hz), 3.18 (2H, broad s).

[0087] Example 585-amino - It compounded according to 2, 4, 6, the 7-tetramethyl-2-(4-methyl piperazino) methyl -2, and the approach of the 3-dihydrobenzofuran above. Yield 76.2%. The 76 to 77 degree C (isopropyl ether) melting point. NMR (CDCl3) delta 1.42 (3H, s) 2.07 (6H, s), 2.09 (3H, s), 2.25 (3H, s), 2.40 (4H, m), 2.48 (1H, d, J= 14.2Hz), 2.58 (1H, d, J= 14.2Hz), 2.50-2.80 (4H, m), 2.80 (1H, d, J= 15.4Hz), 3.11 (1H, d, J= 15.4Hz), 3.25 (2H, braod s).

[0088] Example 595-amino - It compounded according to the approach of the 2, 4, 6, 7-tetramethyl-2-[N-(2-piperidino ethyl) aminomethyl]-2, and 3-dihydrobenzofuran above. Yield 89.2%. Melting point 102 to 104 degree C (dichloromethane-isopropyl ether).
NMR(DMSO-d6) delta 1.44 (3H, s), 1.50-1.62 (6H, m), 1.73 (3H, broad s), 2.06 (3H, s), 2.08 (3H, s) and 2.11 (3H, s), 2.36-2.48 (8H, m), 2.75-2.79 (3H, m), 3.13-3.22 (1H, m).

[0089] Example 605-amino - It compounded according to the approach of the 2, 4, 6, 7-tetramethyl-2-(N-phenyl aminomethyl)-2, and 3-dihydrobenzofuran hydrochloride above. Yield 35.5%. Melting point 162 to 168 degree C (ethanol-ether).
NMR delta (DMSO-d6) 1.45 (3H, s) 2.00 (3H, s), 2.20 (3H, s), 2.22 (3H, s), 2.90 (1H, d, J= 16.4Hz), 3.22 (1H, d, J= 16.4Hz), 3.31 (2H, s), 6.61 (1H, t, J= 7.8Hz), 6.74 (2H, d, J= 7.8Hz), 7.08 (2H, t, J= 7.8Hz), 9.78 (3H, broad s).

[0090] Example 615-amino-2-(N-benzyl aminomethyl)-2, 4 and 6, 7-tetramethyl - It compounded according to the approach of the 2 and 3-dihydrobenzofuran dihydrochloride above. Yield 64.7%. Melting point 228 to 232 degree C (decomposition) (ethanol-ether).
NMR delta (DMSO-d6) 1.48 (3H, s) 2.07 (3H, s), 2.22 (3H, s), 2.23 (3H, s), 2.93 (1H, d, J= 16.2Hz), 3.10 (2H, s), 3.41 (1H, d, J= 16.2Hz), 4.19 (2H, s), 7.38-7.42 (3H, m), and 7.60- 7.65 (2H, m) and 9.70 (3H, broad s).

[0091] Example 625-amino - It compounded according to the approach of the 2, 4, 6, 7-tetramethyl-2-(N-phenethyl aminomethyl)-2, and 3-dihydrobenzofuran dihydrochloride above. Yield 63.1%. Melting point 178 to 181 degree C (ethanol).
NMR delta (DMSO-d6) 1.52 (3H, s), 2.08 (3H, s), 2.23 (3H, s), 2.24 (3H, s), 2.95-3.50 (8H, s), 7.22-7.38 (5H, m), and 9.19 and 9.72 (3H, broad s).

[0092] Example 635-amino - It compounded according to the approach of the 2, 4, 6, 7-tetramethyl-2-[N-(4-phenyl butyl) aminomethyl]-2, and 3-dihydrobenzofuran dihydrochloride above. Yield 72.6%. Melting point 201 to 202 degree C (ethanol-ether).
NMR delta (DMSO-d6) 1.50 (3H, s) 1.53-1.74 (4H, m), 2.07 (3H, s), 2.24 (6H, s), 2.59 (2H, t, J= 7.0Hz), 2.91-3.00 (3H, m), 3.22 (2H, s) and 3.43 (1H, d, J= 15.8Hz), 7.16-7.29 (5H, m), and 9.08 and 9.88 (3H, broad s).

[0093] Example 645-amino - It compounded according to the approach of the 2, 4, 6, 7-tetramethyl-2-[N-(3-pyridyl methyl) aminomethyl]-2, and 3-dihydrobenzofuran 3 hydrochloride above. Yield 54.6%. Melting point 208 to 213 degree C (decomposition) (ethanol-ether).

NMR delta (DMSO-d6) 1.51 (3H, s) 2.09 (3H, s), 2.23 (6H, s) 2.95 (1H, d, J= 16.0Hz), 3.28 (2H, s) 3.50 (1H, d, J= 16.0Hz), 4.43 (2H, s), 7.97 (1H, dd, J= 5.4Hz, 8.0Hz), 8.74 (1H, d, J= 8.0Hz), 8.88 (1H, d, J= 5.4Hz), 9.13 (1H, s), 9.93 (3H, broad s).

[0094] Example 655-amino-2-(1-imidazolyl) methyl [- 2, 4, 6, 7-tetramethyl / - To 2 and the toluene (30ml) suspension of 3-dihydrobenzofuran (3.12g, 10mmol) / An imidazole (10.0g, 147mmol) is added, It heated at 200 degrees C among the autoclave for 15 hours.] - 2, 4, 6, 7-tetramethyl - 2 and 3-dihydrobenzofuran dihydrochloride 2-bromomethyl-5-formylamino Reaction mixture distilled off the solvent after rinsing desiccation. residue is melted to a methanol (30ml) -- 6N-sodium-hydroxide water is added -- heating reflux was carried out for 1 hour. Reaction mixture is diluted with water, Ethyl acetate extracted the product. An extract is the rinsing desiccation back, The solvent was distilled off. A silica gel column chromatography (a chloroform-methanol and 95:5) refines residue, After considering as a hydrochloride, it recrystallized [isopropyl ether / ethanol-] and 1.3g (yield 37.8%) of specified substance was obtained. The 278 to 283 degree C (decomposition) melting point. NMR (DMSO-d6) delta 1.41 (3H, s) 2.08 (3H, s), 2.24 (6H, s) 3.09 (1H, d, J= 16.2Hz), 3.23 (1H, d, J= 16.2Hz), 4.54 (2H, s), 7.66 (1H, d, J= 1.6Hz), 7.73 (1H, d, J= 1.6Hz), 9.19 (1H, s), 10.8 (2H, broad s).

[0095] Example 665-amino - It compounded according to 2, 4, 6, the 7-tetramethyl-2-(4-phenyl piperazino) methyl -2, and the approach of the 3-dihydrobenzofuran above. Yield 18.3%. Melting point 94 to 95 degree C (isopropyl ether). NMR (CDCl3) delta 1.45 (3H, s), 2.08 (6H, s), 2.12 (3H, s), 2.55-2.90 (8H, m), 2.90-3.50 (6H, m), and 6.80- 7.00 (3H, m) and 7.25 (2H, m).

[0096] Example 675-amino - It compounded according to 2, 4, 6, the 7-tetramethyl-2-(4-phenyl piperidino) methyl -2, and the approach of the 3-dihydrobenzofuran above. Yield 57.5%. Melting point 112 to 113 degree C (isopropyl ether). NMR (CDCl3) delta 1.47 (3H, s) 1.75 (4H, m), 2.09 (6H, s), 2.13 (3H, s), 2.15-2.50 (4H, m), 2.54 (1H, d, J= 14.0Hz), 2.63 (1H, d, J= 14.0Hz), 2.84 (1H, d, J= 15.2Hz), 2.99 (1H, m), 3.15 (1H, d, J= 15.2Hz), 3.19 (2H, braod s).7.27 (5H, m).

[0097] Example 685-amino - It compounded according to the approach of the 2, 4, 6, 7-tetramethyl-2-[4-(diphenyl methyl) piperazino methyl]-2, and 3-dihydrobenzofuran dihydrochloride above. Yield 17.7%. Melting point 193 to 196 degree C (decomposition) (ethanol-ether).

NMR delta (DMSO-d6) 1.50 (3H, s), 1.99 (6H, s), 2.21 (3H, s), and 3.03- 3.51 (12H, m), 5.20 (1H, broad s), and 7.33- 7.45 (6H, m) and 7.68 (4H, broad s).

[0098] Example 695-amino-2-benzyloxymethyl [- 2, 4, 6, 7-tetramethyl / - Benzyl alcohol (20ml) and sodium hydride (60% of purity 1.0 g 25mmol) are added to 2 and 3-dihydrobenzofuran (2.0g, 6.4mmol), / It heated at 180 degrees C among the autoclave for 18 hours.] - 2, 4, 6, 7-tetramethyl - 2 and 3-dihydrobenzofuran hydrochloride 2-bromomethyl-5-formylamino Reaction mixture is diluted with the water after cooling, Ethyl acetate extracted the product. An extract is the rinsing desiccation back, The solvent was distilled off. A silica gel column chromatography (isopropyl ether) refines residue, After considering as a hydrochloride, it was made to crystallize from ethanol-isopropyl ether and 0.68g (yield 30.5%) of specified substance was obtained. Melting point 195 to 200 degree C. NMR (DMSO-d6) delta 1.40 (3H, s), 2.05 (3H, s), 2.22 (6H, s), 2.88 (1H, d, J= 15.8Hz), 3.17 (1H, d, J= 15.8Hz), 3.51 (2H, s), 4.56 (2H, s), 7.31 (5H, m), 9.71 (2H, braod s).

[0099] Example 705-amino-2-methoxy - 2, 4, 6, 7-tetramethyl - It compounded according to the approach of the 2 and 3-dihydrobenzofuran hydrochloride above. Yield 49.6%. Melting point 180 to 182 degree C (ethanol-isopropyl ether). NMR (DMSO-d6) delta 1.37 (3H, s), 2.04 (3H, s), 2.22 (6H, s), 2.85 (1H, d, J= 16.0Hz), 3.14 (1H, d, J= 16.0Hz), 3.31 (3H, s), 3.43 (2H, s), 9.77 (2H, braod s).

[0100] Example 715-amino - It compounded according to the approach of the 2, 4, 6, 7-tetramethyl-2-[2-(dimethylamino) ethoxy methyl]-2, and 3-dihydrobenzofuran dihydrochloride above. Yield 67.8%. ****.

NMR delta(DMSO-d6):1.40 (3H, s), 2.02 (3H, s), 2.21 (3H, s), 2.23 (3H, s) and 2.69 (2H, broad s), and 2.81- 3.44 (12H, m) and 9.79 (2H, broad s).

[0101] Example 725-formylamino [- 2, 3-dihydrobenzofuran (6.0g)] - 2, 4, 6, 7-tetramethyl-2-phenyl thiomethyl - 2 and 3-dihydrobenzofuran 2-bromomethyl-5-formylamino - 2, 4, 6, 7-tetramethyl In the dimethylformamide (50ml) solution of 19.2mmol(s) and a thiophenol Sodium

hydride (60% of purity, 1.0 g, 21.1mmol) is added, It stirred at 80 degrees C under the argon ambient atmosphere for 1 hour. Reaction mixture is diluted with the water after cooling, Ethyl acetate extracted the product. An extract is the rinsing desiccation back, The solvent was distilled off. After the silica gel column chromatography (isopropyl ether-ethyl acetate, 1:1) refined residue, it recrystallized [hexane / isopropyl ether-], and 5.54g (yield 83.3%) of specified substance was obtained. Melting point 130 to 131 degree C. NMR (CDCl3) delta 1.55 (1.5H, s) 1.56 (1.5H, s), 2.00 (3H, s), 2.06 (1.5H, s), 2.09 (1.5H, s), 2.11 (1.5H, s), 2.14 (1.5H, s), 2.91 (1H, d, J= 15.8Hz), 3.23 (0.5H, d, J= 15.8Hz) 3.43 (0.5H, d, J= 15.8Hz), 7.97 (0.5H, d, J= 12.0Hz) 3.27 (2H, s), 6.74 (0.5H, broad s), 6.84 (0.5H, d, J= 12.0Hz), 7.15-7.40 (5H, m), 8.40 (0.5H, 1.4Hz). [0102] Example 732-(4-fluoro phenyl) thiomethyl-5-formylamino - 2, 4, 6, 7-tetramethyl - It compounded according to the approach of the 2 and 3-dihydrobenzofuran above. Yield 95.6%. Oily. NMR (CDCl3) delta 1.53 (1.5H, s) 1.55 (1.5H, s), 2.05 (3H, s), 2.06 (1.5H, s), 2.11 (3H, s), 2.14 (1.5H, s) 2.91 (1H, d, J= 15.8Hz), 3.21 (2H, s) 3.22 (0.5H, d, J= 15.8Hz), 3.25 (0.5H, d, J= 15.8Hz) 6.74 (0.5H, broad s), 6.82 (0.5H, d, J= 12.2Hz), 6.95 (2H, t, J= 9.0Hz), 7.36 (2H, dd, J=5.2Hz and 9.0Hz), 7.97 (0.5H, d, J= 12.2Hz), 8.40 (0.5H, d, J= 1.6Hz).

[0103] Example 745-formylamino-2-(4-hydroxyphenyl) thiomethyl - 2, 4, 6, 7-tetramethyl - It compounded according to the approach of the 2 and 3-dihydrobenzofuran above. Yield 93.1%. Oily. NMR (CDCl3) delta 1.51 (1.5H, s) 1.53 (1.5H, s), 1.99 (1.5H, s), 2.01 (1.5H, s), 2.03 (1.5H, s), 2.07 (1.5H, s), 2.10 (1.5H, s), 2.14 (1.5H, s), 2.84 (0.5H, d, J= 15.4Hz) 2.87 (0.5H, d, J= 15.8Hz), 3.10 (0.5H, d, J= 15.4Hz) 3.11 (0.5H, d, J= 15.8Hz), 3.20 (0.5H, d, J= 15.8Hz) 3.21 (0.5H, d, J= 15.8Hz), 3.22 (0.5H, d, J= 15.4Hz) 3.23 (0.5H, d, J= 15.8Hz), 6.01 (0.5H, broad s) 6.15 (0.5H, broads), 6.70 (2H, m), 6.81 (0.5H, broads), 6.85 (0.5H, broad s), 7.25 (2H, m), 7.95 (0.5H, d, J= 11.8Hz), 8.39 (0.5H, d, J= 1.6Hz).

[0104] Example 755-formylamino - 2, 4, 6, 7-tetramethyl-2-(1-methyl-2-imidazolyl) thiomethyl - It compounded according to the approach of the 2 and 3-dihydrobenzofuran above. Yield 88.6%. Oily. NMR (CDCl3) delta 1.53 (1.5H, s) 1.55 (1.5H, s), 1.97 (1.5H, s), 2.03 (1.5H, s), 2.04 (1.5H, s), 2.10 (3H, s), 2.14 (1.5H, s), 2.89 (1H, d, J= 15.6Hz), 3.18 (0.5H, d, J= 15.6Hz) 3.24 (0.5H, d, J= 15.6Hz), 3.47 (2H, s), 3.49 (1.5H, s), 3.52 (1.5H, s), 6.87 (1H, m), 6.99 (0.5H, d, J= 12.0Hz), 7.00 (1H, m), 7.11 (0.5H, broad s), 7.95 (0.5H, d, J= 12.0Hz), 8.37 (0.5H, d, J= 1.4Hz).

[0105] Example 762-(2-benzothiazolyl) thiomethyl-5-formylamino - 2, 4, 6, 7-tetramethyl - It compounded according to the approach of the 2 and 3-dihydrobenzofuran above. Yield 88.2%. Melting point 190 to 192 degree C (isopropyl ether). NMR (CDCl3) delta 1.64 (3H, s) 2.00 (3H, s), 2.07 (1.5H, s), 2.10 (1.5H, s), 2.11 (1.5H, s), 2.14 (1.5H, s) 2.99 (1H, d, J= 15.8Hz), 3.27 (0.5H, d, J= 15.8Hz) 3.29 (0.5H, d, J= 15.8Hz), 3.78 (0.5H, d, J= 15.4Hz) 3.79 (0.5H, d, J= 15.4Hz), 3.87 (0.5H, d, J= 15.4Hz) 3.88 (0.5H, d, J= 15.4Hz), 7.97 (0.5H, d, J= 12.0Hz) 6.73 (0.5H, broad s), 6.75 (0.5H, d, J= 12.0Hz), 7.20-7.50 (2H, m), 7.70-7.85 (2H, m), 8.40 (0.5H, d, J= 1.6Hz).

[0106] Example 775-formylamino - 2, 4, 6, 7-tetramethyl-2-(4-pyridyl) thiomethyl - It compounded according to the approach of the 2 and 3-dihydrobenzofuran above. Yield 71.6%. Oily. NMR (CDCl3) delta 1.59 (1.5H, s) 1.61 (1.5H, s), 1.97 (3H, s), 2.08 (1.5H, s), 2.10 (1.5H, s), 2.13 (1.5H, s), 2.14 (1.5H, s), 2.98 (1H, d, J= 16.0Hz), 3.25 (0.5H, d, J= 16.0Hz) 3.30 (0.5H, d, J= 16.0Hz), 3.31 (2H, s) 7.00 (0.5H, d, J= 12.0Hz), 7.05 (0.5H, broads) 7.17 (2H, dd, J=1.6Hz and 6.2Hz), 7.98 (0.5H, d, J= 12.0Hz), 8.36 (2H, dd, J=1.6Hz and 6.2Hz), 8.37 (0.5H, d, J= 1.6Hz).

[0107] Example 782-benzyl thiomethyl-5-formylamino - 2, 4, 6, 7-tetramethyl - It compounded according to the approach of the 2 and 3-dihydrobenzofuran above. Yield 83.5%. Oily. NMR (CDCl3) delta 1.49 (1.5H, s) 1.50 (1.5H, s), 2.08 (1.5H, s), 2.12 (6H, s), 2.16 (1.5H, s), 2.71 (1H, d, J= 13.4Hz) 2.77 (1H, d, J= 13.4Hz), 2.86 (1H, d, J= 15.0Hz) 3.18 (1H, d, J= 15.0Hz), 3.74 (1H, d, J= 13.2Hz) 3.18 (1H, d, J= 13.2Hz), 6.76 (0.5H, broads), 6.87 (0.5H, d, J= 12.0Hz), 7.30 (5H, m), 7.98 (0.5H, d, J= 12.0Hz), 8.40 (0.5H, d, J= 1.4Hz).

[0108] Example 795-formylamino - 2, 4, 6, 7-tetramethyl-2-propyl thiomethyl - It compounded according to the approach of the 2 and 3-dihydrobenzofuran above. Yield 93.0%. Oily. NMR (CDCl3) delta 0.96 (3H, t, J= 7.4Hz), 1.52 (1.5H, s), 1.54 (1.5H, s), 1.60 (2H, m), 2.08 (3H, s), 2.10 (1.5H, s), 2.12 (1.5H, s), 2.13 (1.5H, s), 2.16 (1.5H, s), 2.58 (2H, dt, J=7.2 and 1.2Hz), 2.82 (1H, s), 2.84 (1H, s), 2.89 (1H, d, J= 15.8Hz), 3.22 (0.5H, d, J= 15.8Hz) 3.24 (0.5H, d, J= 15.8Hz), 6.77 (0.5H, broad s), 6.85 (0.5H, d, J= 12.0Hz), 7.97 (0.5H, d, J= 12.0Hz), 8.40 (0.5H, d, J= 1.6Hz).

[0109] Example 805-formylamino-2-(2-hydroxyethyl) thiomethyl - 2, 4, 6, 7-tetramethyl - It compounded according to the approach of the 2 and 3-dihydrobenzofuran above. Yield 57.2%. Oily. NMR (CDCl3) delta 1.52 (1.5H, s) 1.54 (1.5H, s), 2.09 (3H, s), 2.11 (1.5H, s), 2.12 (1.5H, s), 2.13 (1.5H, s), 2.16 (1.5H, s), 2.29 (0.5H, t, J= 6.4Hz), 2.35 (0.5H, t, J= 6.4Hz) 2.80 (2H, dt, J=7.2 and 1.2Hz), 2.87 (0.5H, s), 2.89 (1H, s), 2.91 (1H, d, J= 15.4Hz), 3.20 (0.5H, d, J= 15.4Hz) 3.22 (0.5H, d, J= 15.4Hz), 3.73 (2H, m), 6.78 (0.5H, broads), 6.80 (0.5H, d, J= 12.0Hz), 7.97 (0.5H, d, J= 12.0Hz), 8.38(0.5H, d, J= 1.4Hz). [0110] Example It compounded according to the approach of the 813-[(5-formylamino - 2, 4, 6, 7-tetramethyl - 2 and 3-dihydrobenzofuran-2-IRU) methylthio] propionic-acid above. Yield 94.7%. Oily. NMR (CDCl3) delta 1.52 (1.5H, s) 1.54 (1.5H, s), 2.08 (3H, s), 2.09 (3H, s), 2.12 (1.5H, s), 2.14 (1.5H, s) 2.64 (2H, t, J= 7.0Hz), 2.86 (2H, t, J= 7.0Hz), 2.87 (2H, s), 2.90 (1H, d, J= 15.4Hz), 3.22 (1H, d, J= 15.4Hz), 6.50 (0.5H, broad s), 6.95 (0.5H, broad s), 7.96 (0.5H, broad s), 8.38(0.5H, d, J= 1.6Hz). [0111] example 825-formylamino -2, 4 and 6, and 7-tetramethyl -2, 3-dihydrobenzofuran-2-IRUFE nil sulfoxide 5-formylamino -2, 4 and 6, 7-tetramethyl-2-phenyl thiomethyl-2, and 3-dihydrobenzofuran (2.3g, 6.7mmol) is melted to a methanol (20ml) -- the 1M-sodium metaperiodate water solution (20ml) was added, and was stirred for 3 hours. Reaction mixture was diluted with water and ethyl acetate extracted the purification object. The extract distilled off the solvent after rinsing desiccation. Residue was crystallized from isopropyl ether-ethyl acetate and 1.54g (yield 64.0%) of specified substance was obtained. Melting point 112 to 115 degree C. NMR (CDCl3) delta 1.62 (3H, s) 2.08 (3H, s), 2.12 (1.5H, s), 2.14 (1.5H, s), 2.16 (1.5H, s), 2.18 (1.5H, s) and 3.00- 3.40 (4H, m) and 6.78 (1H, m) -- 7.45-7.70 (5H, m), 7.96 (0.25H, d, J= 12.0Hz), 7.99 (0.25H, d, J= 12.0Hz), 8.40 (0.25H, d, J= 1.4Hz), 8.42 (0.25H, d, J= 1.4Hz).

[0112] example 835-formylamino -2, 4 and 6, and 7-tetramethyl -2, 3-dihydrobenzofuran-2-IRUFE nil sulfone 5-formylamino -2, 4 and 6, 7-tetramethyl-2-phenyl thiomethyl-2, and 3-dihydrobenzofuran (2.1g, 6.2mmol) is melted to a methanol (20ml) -- the 2M-sodium metaperiodate water solution (20ml) was added, and heating reflux was carried out for 3 hours. Reaction mixture was diluted with water and ethyl acetate extracted the purification object. An extract is the rinsing desiccation back, The solvent was distilled off. Residue was crystallized from isopropyl ether-ethyl acetate and 1.40g (yield 65.9%) of specified substance was obtained. Melting point 154 to 155 degree C. NMR (CDCl3) delta 1.70 (1.5H, s) 1.71 (1.5H, s), 1.81 (1.5H, s), 1.84 (1.5H, s), 2.05 (1.5H, s), 2.07 (1.5H, s), 2.12 (1.5H, s), 2.14 (1.5H, s), 3.01 (1H, d, J= 15.6Hz) 3.56 (1H, s), 3.58 (1H, s) 3.62 (0.5H, d, J= 15.6Hz), 3.67 (0.5H, d, J= 15.6Hz) 6.71 (0.5H, broad s), 6.74 (0.5H, d, J= 12.0Hz), 7.15-7.70 (3H, m), 7.89 (2H, m), 7.96 (0.5H, d, J= 12.0Hz), 8.40 (0.5H, d, J= 1.6Hz).

[0113] Example 845-amino - 2, 4, 6, 7-tetramethyl-2-(2-phenylethyl)-2, 3-dihydrobenzofuran 5-acetylamino - 2, 4, 6, 7-tetramethyl-2-(2-phenylethyl)-2, 3-dihydrobenzofuran (0.7g) 6N-sodium-hydroxide water solution (3ml) is added to the methanol (3ml) solution of 2.1mmol(s), It heated at 200 degrees C in the autoclave for 18 hours. Reaction mixture is diluted with water, Ethyl acetate extracted the product. It is rinsing about an extract, It condenses after desiccation, The silica gel column chromatography (isopropyl ether-ethyl acetate and 2:1) refined residue. The obtained rough crystal was ******ed from the hexane and 0.32g (yield 54.5%) of specified substance was obtained. Melting point 45 to 46 degree C. NMR (CDCl3) delta 1.47 (3H, s) 2.03 (2H, m), 2.07 (3H, s), 2.09 (3H, s), 2.14 (3H, s), 2.76 (2H, m), 2.92 (1H, d, J= 15.4Hz), 3.00 (2H, broad s), 3.07 (1H, d, J= 15.4Hz), 7.10-7.30 (5H, m).

[0114] Example 855-amino - It compounded according to the approach of the 2, 4, 6, 7-tetramethyl-2-[2-(4-fluoro phenyl) ethyl]-2, and 3-dihydrobenzofuran above. Yield 54.6%. Melting point 62 to 63 degree C (hexane). NMR (CDCl3) delta 1.47 (3H, s) 1.98 (2H, m), 2.10 (3H, s), 2.14 (3H, s), 2.19 (3H, s), 2.72 (2H, m), 2.90 (1H, d, J= 14.0Hz), 3.00 (2H, broad s), 3.05 (1H, d, J= 14.0Hz), 6.95 (2H, m), 7.13 (2H, m).

[0115] Example 86 methyl 3-[5-amino -2, 4 and 6, 7-tetramethyl-2, and 3-dihydrobenzofuran-2-IRU] acrylate hydrochloride 3-[5-acetylamino -2, 4 and 6, and 7-tetramethyl-2.3-dihydrobenzofuran-2-IRU] ethyl-acrylate ester (0.5g, 1.58mmol) is melted to a methanol (5ml), Concentrated hydrochloric acid (5ml) was added and heating reflux was carried out for 1 hour. The crystal which cooled reaction mixture and deposited is filtered, The obtained rough crystal

was ******ed from ethanol-isopropyl ether, and 0.35g (yield 74.7%) of specified substance was obtained. Melting point 225 to 234 degree C (decomposition). NMR (DMSO-d6) delta 1.58 (3H, s) 2.11 (3H, s), 2.19 (3H, s), 2.21 (3H, s), 3.12 (1H, d, J= 15.0Hz), 3.24 (1H, d, J= 15.0Hz), 3.65 (3H, s), 5.93 (1H, d, J= 16.0Hz), 7.04 (1H, d, J= 16.0Hz), 9.50 (2H, broad s).

[0116] Example 875-amino-2-bromomethyl - 2, 4, 6, 7-tetramethyl - It compounded according to the approach of the 2 and 3-dihydrobenzofuran hydrochloride above. Yield 90.2%. Melting point 235 to 245 degree C (decomposition) (ethanol-isopropyl ether). NMR (DMSO-d6) delta 1.53 (3H, s), 2.04 (3H, s), 2.23 (3H, s), 2.24 (3H, s), 3.03 (1H, d, J= 16.0Hz), 3.27 (1H, d, J= 16.0Hz), 3.77 (2H, s), 9.85 (2H, broad s).

[0117] Example 885-amino-2-phenyl thiomethyl - 2, 4, 6, 7-tetramethyl - It compounded according to the approach of the 2 and 3-dihydrobenzofuran hydrochloride above. Yield 94.5%. Melting point 130 to 131 degree C (ethanol-isopropyl ether). NMR (DMSO-d6) delta 1.51 (3H, s), 1.87 (3H, s), 2.19 (3H, s), 2.20 (3H, s), 2.99 (1H, d, J= 15.8Hz), 3.22 (1H, d, J= 15.8Hz), 3.38 (2H, s), and 7.10- 7.40 (5H, m) and 9.69 (2H, broads).

[0118] Example 895-amino-2-(4-fluoro phenyl) thiomethyl - 2, 4, 6, 7-tetramethyl - It compounded according to the approach of the 2 and 3-dihydrobenzofuran hydrochloride above. Yield 80.9%. Melting point 204 to 210 degree C (decomposition) (ethanol-isopropyl ether). NMR (DMSO-d6) delta 1.49 (3H, s) 1.84 (3H, s), 2.19 (3H, s), 2.20 (3H, s), 2.98 (1H, d, J= 15.8Hz), 3.21 (1H, d, J= 15.8Hz) 3.31 (1H, d, J= 14.0Hz), 3.39 (1H, d, J= 14.0Hz), 7.13 (2H, t, J= 9.0Hz), 7.38 (2H, dd, J=9.0 and 5.4Hz), 9.67 (2H, broad s).

[0119] Example 905-amino-2-(4-hydroxyphenyl) thiomethyl - 2, 4, 6, 7-tetramethyl - It compounded according to the approach of the 2 and 3-dihydrobenzofuran hydrochloride above. Yield 96.2%. Melting point 230 to 236 degree C (decomposition) (ethanol-isopropyl ether). NMR (DMSO-d6) delta 1.46 (3H, s) 1.91 (3H, s), 2.18 (6H, s) 2.94 (1H, d, J= 15.8Hz), 3.20 (1H, d, J= 15.8Hz), 3.20 (2H, s), 6.70 (2H, d, J= 8.6Hz), 7.19 (2H, d, J= 8.6Hz), 9.45 (2H, broad s), 9.56 (1H, s).

[0120] Example 915-amino-2-(1-methyl imidazole-2-IRU) thiomethyl - 2, 4, 6, 7-tetramethyl - It compounded according to the approach of the 2 and 3-dihydrobenzofuran dihydrochloride above. Yield 65.3%. Melting point 220 to 225 degree C (decomposition) (ethanol-isopropyl ether). NMR (DMSO-d6) delta 1.50 (3H, s) 1.72 (3H, s), 2.19 (3H, s), 2.24 (3H, s), 3.05 (1H, d, J= 16.2Hz), 3.29 (1H, d, J= 16.2Hz) 3.50 (3H, s), 3.56 (1H, d, J= 14.6Hz), 3.84 (1H, d, J= 14.6Hz), 7.71 (1H, d, J= 1.8Hz), 7.75 (1H, d, J= 1.8Hz), 10.2 (2H, broad s).

[0121] Example 925-amino-2-(2-benzothiazolyl) thiomethyl - 2, 4, 6, 7-tetramethyl - It compounded according to the approach of the 2 and 3-dihydrobenzofuran hydrochloride above. Yield 89.1%. Melting point 204 to 208 degree C (decomposition) (ethanol-isopropyl ether). NMR (DMSO-d6) delta 1.58 (3H, s) 1.76 (3H, s), 2.16 (3H, s), 2.21 (3H, s), 3.08 (1H, d, J= 15.8Hz), 3.28 (1H, d, J= 15.8Hz) 3.79 (1H, d, J= 14.6Hz), 3.88 (1H, d, J= 14.6Hz), 7.37 (1H, t, J= 7.6Hz), 7.47 (1H, t, J= 7.6Hz), 7.78 (1H, d, J= 7.6Hz), 8.01 (1H, d, J= 7.6Hz), 9.65 (2H, broad s).

[0122] Example 935-amino-2-benzyl thiomethyl - 2, 4, 6, 7-tetramethyl - It compounded according to the approach of the 2 and 3-dihydrobenzofuran hydrochloride above. Yield 74.1%. Melting point 170 to 172 degree C (ethanol-isopropyl ether). NMR (DMSO-d6) delta 1.44 (3H, s) 2.07 (3H, s), 2.23 (6H, s), 2.80 (2H, s), 2.93 (1H, d, J= 16.0Hz), 3.13 (1H, d, J= 16.0Hz), 3.77 (1H, d, J= 13.8Hz), 3.87 (1H, d, J= 13.8Hz), 7.29 (5H, m), 9.77 (2H, broad s).

[0123] Example 945-amino - 2, 4, 6, 7-tetramethyl-2-(4-pyridyl) thiomethyl - It compounded according to the approach of the 2 and 3-dihydrobenzofuran above. Yield 80.4%. Melting point 96 to 97 degree C (ethyl-acetate-isopropyl ether). NMR (CDCl3) delta 1.58 (3H, s) 2.00 (3H, s), 2.05 (3H, s), 2.06 (3H, s), 2.85 (2H, broads), 2.98 (1H, d, J= 15.6Hz) 3.21 (1H, d, J= 15.6Hz), 3.25 (1H, d, J= 14.0Hz), 3.32 (1H, d, J= 14.0Hz), 7.14 (2H, dd, J=4.8 and 2.0Hz), 8.33 (2H, dd, J=4.8 and 2.0Hz).

[0124] Example 955-amino - 2, 4, 6, 7-tetramethyl-2-propyl thiomethyl - It compounded according to the approach of the 2 and 3-dihydrobenzofuran hydrochloride above. Yield 74.6%. Melting point 186 to 188 degree C (ethanol-isopropyl ether). NMR (DMSO-d6) delta 0.97 (3H, t, J= 7.4Hz), 1.53 (3H, s) 1.40-1.70 (2H, m), 2.09 (3H, s), 2.50 (6H, s), 2.45-2.60 (2H, m), 2.82 (2H, s), 2.88 (1H, d, J= 15.4Hz), 3.28 (1H, d, J= 15.4Hz), 10.10 (2H, broad s).

[0125] Example 965-amino-2-(2-hydroxyethyl) thiomethyl - 2, 4, 6, 7-tetramethyl - It compounded according to the approach of the 2 and 3-dihydrobenzofuran above. Yield 32.3%. Melting point 108 to 109 degree C (ethyl-acetate-isopropyl ether). NMR (CDCl3) delta 1.51 (3H, s) 2.07 (3H, s), 2.08 (3H, s), 2.11 (3H, s), 2.80 (1H, broads), 2.81 (2H, t, J= 5.4Hz) 2.82 (1H, d, J= 15.0Hz), 2.90 (1H, d, J= 15.0Hz), 2.92 (1H, d, J= 15.4Hz), 3.19 (1H, d, J= 15.4Hz), 3.20 (2H, broad s), 3.73 (2H, t, J= 5.4Hz).
[0126] Example It compounded according to the approach of the 973-[(5-amino - 2, 4, 6, 7-tetramethyl - 2 and 3-dihydrobenzofuran-2-IRU) methylthio] propionic-acid above. Yield 77.5%. Melting point 139 to 140 degree C (ethyl-acetate-isopropyl ether). NMR (CDCl3) delta 1.51 (3H, s) 2.07 (6H, s), 2.09 (3H, s), 2.64 (2H, t, J= 6.8Hz), 2.80 (1H, d, J= 14.0Hz), 2.87 (1H, d, J= 14.0Hz), 2.88 (2H, t, J= 6.8Hz), 2.91 (1H, d, J= 15.4Hz), 3.20 (1H, d, J= 15.4Hz), 4.90 (3H, broad s).
[0127] Example 985-amino [It compounded according to the approach of the phenyl sulfoxide above.] - 2, 4, 6, 7-tetramethyl - 2 and 3-dihydrobenzofuran-2-IRU Yield 21.0%. Oily. NMR (CDCl3) delta 1.60 (1.5H, s), 1.84 (1.5H, s), 2.04 (1.5H, s), 2.09 (4.5H, s), 2.11 (3H, s), 2.90-3.45 (5.5H, m), 3.69 (0.5H, d, J= 15.8Hz), 7.48 (3H, m), 7.63 (2H, m).
[0128] Example 995-amino [It compounded according to the approach of the phenyl sulfone above.] - 2, 4, 6, 7-tetramethyl - 2 and 3-dihydrobenzofuran-2-IRU Yield 91.7%. Melting point 150 to 151 degree C (ethyl-acetate-isopropyl ether). NMR (CDCl3) delta 1.69 (3H, s) 1.81 (3H, s), 2.02 (3H, s), 2.05 (3H, s), 2.99 (1H, d, J= 15.6Hz), 3.30 (2H, broad s), 3.54 (2H, s), 3.60 (1H, d, J= 15.6Hz), and 7.40- 7.70 (3H, m) and 7.85 (2H, m).
[0129] Example 1005-amino - 2, 2, 6, 7-tetramethyl-4-nitro -It compounded according to the approach of the 2 and 3-dihydrobenzofuran hydrochloride above. Yield 79.6%. Melting point 119 to 121 degree C (ethanol-ether).
NMR delta (CDCl3) 1.48 (6H, s), 2.20 (3H, s), 2.54 (3H, s), 3.42 (2H, s), 8.61 (2H, broads).
[0130] Example 1015-amino - It compounded according to 2, 2, 6, 7-tetramethyl-4-dimethylamino -2, and the approach of the 3-dihydrobenzofuran dihydrochloride above. Yield 64.5%. Melting point 240 to 244 degree C (ethanol).
NMR(DMSO-d6) delta 1.42 (6H, s), 2.02 (3H, s), 2.18 (3H, s), 2.63 (6H, s), 3.17 (2H, s), 4.94 (2H, broad s).
[0131] Example 1025-amino - It compounded according to 2, 2, 4, 7-tetramethyl-6-dimethylamino -2, and the approach of the 3-dihydrobenzofuran hydrochloride above. Yield 63.2%. Melting point 236 to 238 degree C (ethanol).
NMR delta(DMSO-d6): 1.41 (6H, s), 2.10 (3H, s), 2.19 (3H, s), 2.72 (6H, s), 2.96 (2H, s), 9.66 (2H, broad s).
[0132] Example 1035-amino - 2, 2, 4, 6, 7-pentamethyl -2, 3-dihydrobenzofuran 4-amino - 2.0ml of sulfuric acids was added to the dichloromethane (20ml) solution (2, 3, and 5-trimethyl phenol 2.0g (13.2 millimol) and 2-methyl-2-propenol 1.15g (15.8 millimol)), and heating reflux was carried out for bottom 18 hours of an argon ambient atmosphere. Reaction mixture was made into alkalescence with saturation sodium-hydrogencarbonate water, and the organic layer was divided. An organic layer is condensed after rinsing and desiccation, a silica gel column chromatography (it is elution with isopropyl ether) refines residue, the obtained product is ******ed from a hexane, and it is 5-amino. - 460mg (16.9% of yield) of crystals of 2, 2, 4, 6, and 7-pentamethyl coumarane was obtained. The melting point of 110-111 degrees C.
NMR(CDCl3) delta: 1.45 (6H, s), 2.06 (3H, s), 2.09 (3H, s), 2.13 (3H, s), 2.94 (2H, s), 3.26 (2H, broad s).
[0133] Example Concentrated hydrochloric acid (10ml) was added to 1042, 2, 4, 6, 7-pentamethyl-5-phenylamino -2, the 3-dihydrobenzofurans 3 and 5, and the methanol (30ml) solution of a 6-trimethyl-2-(2-methyl-2-propenyl)-4-phenylamino phenol (1.40g, 4.98mmol) under ice-cooling, and the heating reflux of the mixture was carried out for 30 minutes under the argon ambient atmosphere. After cooling reaction mixture, sodium bicarbonate water neutralized, and ethyl acetate extracted. After saturation brine washed the extract, it dried and condensed. Residue was ******ed from isopropyl ether and 0.97g (yield 69.3%) of specified substance was obtained. Melting point 148 to 151 degree C.
NMR (CDCl3) delta 1.49 (6H, s), 2.04 (3H, s), 2.10 (3H, s), 2.12 (3H, s), 2.95 (2H, s), 5.03 (1H,

broad s), 6.42-6.48 (2H, m), 6.64-6.72 (1H, m), 7.08-7.17 (2H, m).
[0134] Example It compounded according to the same approach as 1055-(4-chlorophenylamino)-2, 2, 4 and 6, 7-pentamethyl -2, and the 3-dihydrobenzofuran example 104. Yield 60.0%. Melting point 106 to 107 degree C (isopropyl ether-pentane).
NMR (CDCl3) delta 1.49 (6H, s), 2.02 (3H, s), 2.07 (3H, s), 2.12 (3H, s), 2.95 (2H, s), 5.04 (1H, broad s), 6.36 (2H, d, J= 8.8Hz), 7.06 (2H, d, J= 8.8Hz).
[0135] Example It compounded according to the same approach as 1065-(4-methoxy phenylamino)-2, 2, 4 and 6, 7-pentamethyl -2, and the 3-dihydrobenzofuran example 104. Yield 61.2%. Melting point 117 to 119 degree C (isopropyl ether-pentane).
NMR (CDCl3) delta 1.49 (6H, s), 2.04 (3H, s), 2.09 (3H, s), 2.12 (3H, s), 2.95 (2H, s), 3.73 (3H, s), 4.86 (1H, broad s), 6.41 (2H, d, J= 9.0Hz), 6.73 (2H, d, J= 9.0Hz). [0136] Example of reference 14-amino - in the water (250ml) solution of a 2, 3, and 5-trimethyl phenol sulfanilic acid (49.4g, 258mmol) It is a solid-state, stirring at room temperature. Na2CO3 (g [13.7], 129mmol) It adds little by little. After reaction mixture turns into a uniform solution (you may warm when [a little] not melting) It ice-cooled and the water (50ml) solution of NaNO2 (g [19.4], 280mmol) was added (internal temperature of 10 degrees C or less)., Next, this solution is put into a dropping funnel, It was dropped in about 10 minutes on concentrated hydrochloric acid (46ml) and ice (100g) with the bottom scrambling of ice-cooling (the internal temperature of a dropping funnel is 10 degrees C or less). After dropping termination, Reaction mixture was stirred for 30 minutes, continuing ice-cooling. next, water (250ml), NaOH (56.8g, 142mmol) and 2 and 3, and a 5-trimethyl phenol (35.3g, 259mmol) are put into another reaction container equipped with the mechanical agitator -- previous reaction mixture was dropped in -10 to 5 degrees C with the bottom scrambling of a nitrogen air current (ice is added suitably and it cools so that the temperature of the contents of a dropping funnel may not exceed 10 degrees C.) It is dropped in about 15 minutes. After dropping termination, Reaction mixture was warmed at 50 degrees C, and Na2S2O4 (11.9g, 68.3mmol) was added. Then, reaction mixture is warmed at 80 degrees C, Further, Na2S2O4 (214.2g, 1.23 mols) was equally divided into five, and it was added at intervals of 5 minutes. Reaction mixture is for 30 minutes, It cools, after stirring at this temperature, The depositing crystal was ****(ed). The obtained crystal is rinsed, It recrystallized [isopropyl ether / after desiccation / ethyl-acetate-] and 33.0g (yield 84.2%) of specified substance was obtained. Melting point 153 to 154 degree C.
NMR (CDCl3) delta 2.11 (6H, s), 2.16 (3H, s), 3.55 (3H, broad s), 6.42 (2H, s).
[0137] Example of reference It compounded according to the 24-amino -2 and the approach of 5-dimethylphenol above. Yield 59.7%. Melting point 216 to 220 degree C(water).
NMR (DMSO-d6) delta 1.94 (3H, s), 1.97 (3H, s), 4.06 (2H, broad s), 6.33 (1H, s), 6.38 (1H, s), 8.04 (1H, s).
[0138] Example of reference It compounded according to the 34-amino -3 and the approach of 5-dimethylphenol above. Yield 52.2%. Melting point 190 to 191 degree C(water).
NMR (DMSO-d6) delta 2.01 (6H, s), 3.90 (2H, broad s), 6.28 (2H, s), 8.19 (1H, s).
[0139] example of reference 44-formylamino - 2, 3, and 5-trimethyl phenol 4-amino - a 2, 3, and 5-trimethyl phenol (100g, 662mmol) is melted to a formic acid (500ml) -- heating reflux was carried out for 36 hours. Reaction mixture is poured out into iced water, The depositing crystal is ****(ed), Rinsing, It dried. The obtained rough crystal is ******ed from ethanol, 85.9g (yield 72.5%) of specified substance was obtained. Melting point 219 to 220 degree C. NMR (CDCl3) delta 2.00 (3H, s), 2.03 (6H, s), 6.53 (1H, s), 8.20 (1H, d, J= 1.8Hz), 9.06 (1H, s), 9.15 (1H, broad s).

[0140] Example of reference It compounded according to 54-formylamino -3 and the approach of 5-dimethylphenol above. Yield 70.3%. Melting point 239 degrees C (dichloromethane-isopropyl ether).
NMR (DMSO-d6) delta 2.05 (6H, s), 6.46 (2H, s), 8.19 (1H, s), 9.13 (1H, broad s), 9.16 (1H, s).
[0141] Example of reference 61-acetoxy-4-acetylamino [The acetic anhydride (53ml, 56.2mmol) was dropped with scrambling.] - 2, 3, 5-trimethyl benzene 4-amino - A 2, 3, and 5-trimethyl phenol (26.5g, 17.5mmol) is melted to a pyridine (80ml), After stirring reaction mixture for 1 hour The crystal which poured and deposited in iced water was ****(ed)., A crystal is rinsing, It

recrystallized [ethyl acetate / after desiccation] and 36.5g (yield 88.5%) of specified substance was obtained. Melting point 174 to 175 degree C. NMR (CDCl3) delta 2.00- 2.25 (12H, m), 2.31 (3H, s), and 6.60-6.90 (2H, m).

[0142] Example of reference It compounded according to 71-acetoxy-4-acetylamino -2 and the approach of 3-dimethylbenzene above. Yield 88.3%. Melting point 155 to 156 degree C (dichloromethane-isopropyl ether).

NMR (CDCl3) delta 2.09 (3H, s), 2.14 (3H, s), 2.19 (3H, s), 2.33 (2H, s), 6.86 (1H, d, J= 8.5Hz), 7.05 (1H, broad s), 7.37 (1H, d, J= 8.5Hz).

[0143] Example of reference It compounded according to 81-acetoxy-4-acetylamino -2 and the approach of 5-dimethylbenzene above. Yield 54.9%. Melting point 177 degrees C (dichloromethane-isopropyl ether).

NMR (CDCl3) delta 2.12 (3H, s), 2.16 (3H, s), 2.30 (3H, s), 6.81 (1H, s), 7.02 (1H, broads), 7.57 (1H, s).

[0144] Example of reference 94-acetylamino [The water (150ml) solution of potassium carbonate (27g 195mmol) is added, It stirred at the bottom room temperature of an argon ambient atmosphere for 1 hour.] - 2, 3, 5-trimethyl phenol 1-acetoxy-4-acetylamino - In 2, 3, and the methanol (300ml) solution of 5-trimethyl benzene (66.0g, 324mmol) After adding 1N-hydrochloric acid to reaction mixture and considering as the acescence It diluted with water., The depositing crystal is ****(ed), Rinsing, After desiccation, It recrystallized [isopropyl ether / ethyl-acetate-] and 36.8g (yield 67.9%) of specified substance was obtained. The 189 to 190 degree C (ethyl-acetate-isopropyl ether) melting point. NMR (DMSO-d6) delta 1.98 (3H, s), 1.99 (6H, s), 2.01 (3H, s), 6.50 (1H, s), 8.95 (1H, s), 9.00 (1H, s).

[0145] Example of reference It compounded according to 104-acetylamino -2 and the approach of 3-dimethylphenol above. Yield 40.0%. Melting point 184 to 185 degree C (dichloromethane-isopropyl ether).

NMR (CDCl3) delta 2.13 (3H, s), 2.16 (3H, s), 2.18 (3H, s), 6.66 (1H, d, J= 8.5Hz), 7.01 (1H, d, J= 8.5Hz), 7.22 (1H, broad s), 7.29 (1H, s).

[0146] Example of reference It compounded according to 114-acetylamino -2 and the approach of 5-dimethylphenol above. Yield 92.1%. Melting point 183 degrees C (dichloromethane-isopropyl ether).

NMR (DMSO-d6) delta 1.97 (3H, s), 2.04 (6H, s), 6.58 (1H, s), 6.91 (1H, s), 9.03 (2H, s).

[0147] Example of reference 124-formylamino [Potassium carbonate (74.0g, 0.54 mols) was added to the dimethylformamide (300ml) solution of chlorination metallyl (45.3g, 0.5 mols), and it stirred at 80 degrees C under the argon ambient atmosphere for 3 hours.] - 2, 3, 5-trimethyl-1-(2-methyl-2-propenyloxy) benzene 4-formylamino - 2, 3, and 5-trimethyl phenol (85.5g, 0.48 mols), Reaction mixture is poured out into iced water, The depositing crystal is ****(ed), Rinsing, It dried. It recrystallizes [isopropyl ether] and the obtained rough crystal is the specified substance. 80.0g (yield 71.6%) was obtained. The 144 to 145 degree C melting point. NMR (CDCl3) delta 1.84 (3H, m) 2.17 (3H, s), 2.19 (1.5H, s), 2.22 (3H, s), 2.26 (1.5H, s), 4.40 (1H, s), 4.42 (1H, s), 4.99 (1H, m), 5.11 (1H, broad s), 6.60 (1H, s), 6.75 (1H, m), 7.98 (0.5H, d, J= 12.0Hz), 8.41 (0.5H, s).

[0148] Example of reference 134-acetylamino - It compounded according to the approach of the 2, 3, and 5-trimethyl-1-(2-methyl-2-propenyloxy) benzene above. Yield 92.6%. Melting point 149 to 150 degree C (isopropyl ether). NMR (CDCl3) delta 1.84 and 1.86 (3H, s), 2.14 (3H, s), 2.16 (3H, s), 2.19 (3H, s), 2.20 (3H, s), 4.38 and 4.32 (2H, s), 4.98 (1H, m), and 5.11 (1H, broad s), 6.58 and 6.50 (1H, s), and 6.60 and 6.72 (1H, broad s).

[0149] Example of reference It compounded according to the approach of the 142, 3, and 5-trimethyl-1-(2-methyl-2-propenyloxy) benzene above. Yield 98.9%. Boiling point 108 to 112 degree C (10mmHg). NMR (CDCl3) delta 1.87 (3H, s), 2.17 (3H, s), 2.26 (3H, s), 2.30 (3H, s), 4.42 (2H, s), 5.00 (1H, broad s), 5.15 (1H, broad s), 6.55 (1H, broad s), 6.64 (1H, broad s).

[0150] Example of reference It compounded according to the approach of the 154-acetylamino - 2 and 3-dimethyl-1-(2-methyl-2-propenyloxy) benzene above. Yield 86.2%. Melting point 154 to 156 degree C (dichloromethane-isopropyl ether).

NMR (CDCl3) delta 1.84 (3H, s) 2.16 (3H, s), 2.19 (3H, s), 2.21 (3H, s), 4.41 (2H, s), 4.98 (1H, s),

5.12 (1H, s), 6.70 (1H, d, J= 8.8Hz), 6.89 (1H, broad s), 7.20 (1H, d, J= 8.8Hz).
[0151] Example of reference It compounded according to the approach of the 164-acetylamino - 2 and 5-dimethyl-1-(2-methyl-2-propenyloxy) benzene above. Yield 84.3%. Melting point 128 to 132 degree C (dichloromethane-isopropyl ether).
NMR (CDCl3) delta 1.60 and 2.17 (3H, s), 1.84 (3H, s), 2.20 (6H, s), 4.40 (2H, s), 4.98 (1H, s), 5.11 (1H, s), 6.63 (1H, s), 6.80 (1H, broad s), and 7.28 (1H, s).
[0152] Example of reference It compounded according to the approach of the 174-formylamino - 3 and 5-dimethyl-1-(2-methyl-2-propenyloxy) benzene above. Yield 98.4%. Melting point 128 to 129 degree C (isopropyl ether).
NMR (DMSO-d6) delta 1.77 (3H, s), 2.11 (6H, s), 4.43 (2H, s), 4.95 (1H, s), 5.05 (1H, s), 6.68 (2H, s), 8.22 (1H, s), 9.26 (1H, s).
[0153] Example of reference It compounded according to 184-formylamino -3 and the approach of the 5-dimethyl-2-(2-methyl-2-propenyl)-1-(2-methyl-2-propenyloxy) benzene above. Yield 98.4%. Melting point: 109 degrees C (dichloromethane-isopropyl ether).
NMR (DMSO-d6) delta 1.72 (3H, s) 1.76 (3H, s), 2.01 (3H, s), 2.12 (3H, s), 3.32 (2H, s), 4.30 (1H, s), 4.41 (2H, s), 4.66 (1H, s), 4.93 (1H, s), 5.06 (1H, s), 6.73 (1H, s), 8.22 (1H, s), 9.27 (1H, s).
[0154] example of reference 194-formylamino - 2, 3, and 5-trimethyl-6-(2-methyl-2-propenyl) phenol 4-formylamino - 2, 3, and 5-trimethyl-1-(2-methyl-2-propenyloxy) benzene (80g, 0.34 mols) is melted to N,N-diethylaniline (500ml) -- it heated at 200 degree C for 3 hours. It cools radiationally, A hexane will be added if a crystal begins to deposit, The depositing crystal is **** (ed), 75.2g (yield 94.0%) of specified substance was obtained. It recrystallizes [isopropyl ether / ethyl-acetate-] and a rough crystal is the melting point. The crystal of 163 to 164 degree C was obtained. NMR (CDCl3) delta 1.80 (3H, s) 2.16 (3H, s), 2.17 (1.5H, s), 2.19 (1.5H, s), 2.20 (1.5H, s), 2.21 (1.5H, s), 3.38 (2H, broad s), 4.65 (1H, m), 4.88 (1H, m), 5.16 (0.5H, s), 5.19 (0.5H, s), 6.70 (1H, m), 7.95 (0.5H, d, J= 12.0Hz), 8.42 (0.5H, d, J= 1.8Hz).
[0155] Example of reference 204-acetylamino - It compounded according to the approach of the 2, 3, and 5-trimethyl-6-(2-methyl-2-propenyl) phenol above. Yield 97.7%. Melting point 209 to 210 degree C (ethyl-acetate-isopropyl ether). NMR (CDCl3) delta 1.73 (3H, s), 1.94 (3H, s), 1.99 (6H, s), 2.09 (3H, s), 3.33 (2H, m), 4.28 (1H, broad s), 4.64 (1H, broad s), 7.86 (1H, broad s), 9.00 (1H, s).
[0156] Example of reference It compounded according to the approach of the 212, 3, and 5-trimethyl-6-(2-methyl-2-propenyl) phenol above. Yield 80.6%. Boiling point 124 to 126 degree C (10mmHg). NMR (CDCl3) delta 1.79 (3H, s), 2.14 (3H, s), 2.24 (6H, s), 3.37 (2H, s), 4.74 (1H, m), 4.88 (1H, m), 5.08 (1H, s), 6.63 (1H, s).
[0157] Example of reference It compounded according to the approach of the 224-acetylamino - 2 and 3-dimethyl-6-(2-methyl-2-propenyl) phenol above. Yield 91.8%. Melting point: 149 to 151 degree C (dichloromethane-isopropyl ether).
NMR (CDCl3) delta 1.72 (3H, s), 2.12 (3H, s), 2.16 (3H, s), 2.17 (3H, s), 3.32 (2H, s), 4.89-4.94 (2H, m), 5.39 (1H, s), 6.92 (1H, broad s), 7.00 (1H, s).
[0158] Example of reference It compounded according to the approach of the 234-acetylamino - 2 and 5-dimethyl-6-(2-methyl-2-propenyl) phenol above. Yield 98.7%. Melting point: 183 to 185 degree C (dichloromethane-isopropyl ether).
NMR (CDCl3) delta 1.79 (3H, s), 2.11-2.22 (9H, m), 3.38 (2H, s), 4.60 (1H, s), 4.83 (1H, s), 7.11 (1H, s).
[0159] Example of reference It compounded according to the approach of the 244-formylamino - 3 and 5-dimethyl-2-(2-methyl-2-propenyl) phenol above. Yield 80.8%. Melting point 207 to 209 degree C (isopropyl ether).
NMR (DMSO-d6) delta 1.71 (3H, s), 1.97 (3H, s), 2.04 (3H, s), 3.25 (2H, s), 4.33 (1H, s), 4.65 (1H, s), 6.55 (1H, s), 8.19 (1H, s), 9.09 (1H, s).
[0160] Example of reference It compounded according to 252, 6-screw (2-methyl-2-propenyl)-4-formylamino -3, and the approach of 5-dimethylphenol above. Yield 84.2%. Melting point 169 to 170 degree C (isopropyl ether).
NMR (DMSO-d6) delta 1.72 (6H, s), 1.98 (6H, s), 3.33 (4H, s), 4.28 (2H, s), 4.65 (2H, s), 7.86 (1H, s), 8.20 (1H, s), 9.19 (1H, s).

[0161] Example of reference 262-BUROMO - The toluene (1l.) solution of 3, 5, and 6-trimethyl anisole tert butylamine (73g, 1.0 mols) was cooled at -20-30 degrees C, and the bromine (79.9g, 0.5 mols) was dropped in about 10 minutes with scrambling. next, reaction mixture is cooled at -70--75 degree C -- the 2, 3, and 5-trimethyl phenol (68g, 0.5 mols) was melted and dropped at the methylene chloride of a critical mass. Reaction mixture is this temperature for 30 minutes, After stirring at a room temperature continuously for 3 hours It washes with water, It condensed after desiccation., After putting in sodium hydride (60% of content, 22 g, 0.55 mols) in another reactor and washing 2 to 3 times by the hexane, dimethylformamide (500ml) is added, Under an argon ambient atmosphere, The dimethylformamide (50ml) solution of previous concentration residue was dropped ice-cooling. Reaction mixture is stirred for 30 minutes, Iodomethane (34.2ml, 0.55 mols) is dropped continuously, It stirred for further 1 hour. Reaction mixture is diluted with water, Isopropyl ether extracts a product, Extract, Rinsing, It condensed after desiccation. Concentration residue is distilled by reduced pressure, If the boiling point collects 130-135 degrees C (10mmHg) fractions 32.3g (yield 28.6%) of specified substance was obtained., NMR (CDCl3) delta 2.20 (3H, s), 2.21 (3H, s), 2.34 (3H, s), 3.76 (3H, s), 6.83 (1H, s).

[0162] example of reference 271-(2-methoxy - 3, 4, 6-trimethyl phenyl)-1-phenyl-2-methyl propanol 2-BUROMO - the tetrahydrofuran (20ml) solution of a 3, 5, and 6-trimethyl anisole (3.0g, 13.1mmol) is cooled at -78 degrees C -- n-butyl lithium (a 1.6M hexane solution, 8.2 ml, 13.1mmol) was dropped. Reaction mixture is stirred for 15 minutes at this temperature, Next, the tetrahydrofuran (5ml) solution of isobutyryl benzene (1.94g, 13.1mmol) is dropped, It stirred for 30 more minutes at the room temperature. Reaction mixture is diluted with water, Isopropyl ether extracted the product. An extract is rinsing, After desiccation, It condenses and residue is crystallized from a hexane, 3.13g (yield 80.2%) of specified substance was obtained. Melting point 80 to 81 degree C. NMR (CDCl3) delta 0.88 (3H, d, J= 6.6Hz), 1.05 (3H, d, J= 6.4Hz), 2.07 (3H, s), 2.18 (3H, s), 2.58 (3H, s), 2.82 (1H, qq, J=6.4Hz and 6.6Hz), 2.90 (3H, s), 6.18 (1H, broad s), 6.75 (1H, s), 7.10-7.30 (3H, m), 7.40-7.50 (2H, m).

[0163] Example of reference It compounded according to the approach of the 281-(4-fluoro phenyl)-1-(2-methoxy - 3, 4, 6-trimethyl phenyl)-2-methyl propanol above. Yield 97.9%. Melting point 102 to 103 degree C (hexane). NMR (CDCl3) delta 0.88 (3H, d, J= 6.6Hz), 1.02 (3H, d, J= 6.4Hz), 2.08 (3H, s), 2.19 (3H, s), 2.53 (3H, s) 2.80 (1H, qq, J=6.4Hz and 6.6Hz), 2.97 (3H, s), 6.23 (1H, broad s), 6.75 (1H, s), 6.95 (2H, t, J= 8.8Hz), 7.40 (2H, dd, J=8.8 and 5.4Hz).

[0164] Example of reference It compounded according to the approach of the 291-(2-methoxy - 3, 4, 6-trimethyl phenyl)-1-(4-methylphenyl)-2-methyl propanol above. Yield 80.6%. Melting point 103 to 104 degree C (hexane). NMR (CDCl3) delta 0.89 (3H, d, J= 6.6Hz), 1.03 (3H, d, J= 6.4Hz), 2.09 (3H, s), 2.19 (3H, s), 2.30 (3H, s), 2.56 (3H, s), 2.82 (1H, qq, J=6.4Hz and 6.6Hz), 2.95 (3H, s), 6.18 (1H, broad s), 6.75 (1H, s), 7.07 (2H, d, J= 8.2Hz), 7.32 (2H, d, J= 8.2Hz).

[0165] Example of reference It compounded according to the approach of the 301-(2-methoxy - 3, 4, 6-trimethyl phenyl)-1-(4-propyl phenyl)-2-methyl propanol above. Yield 74.6%. Melting point 59 to 60 degree C (hexane). NMR (CDCl3) delta 0.87 (3H, t, J= 6.4Hz), 0.90 (3H, d, J= 6.6Hz) 1.03 (3H, d, J= 6.4Hz), 1.60 (2H, sextet, 6.4Hz) 2.08 (3H, s), 2.18 (3H, s), 2.54 (2H, t, J= 6.4Hz), 2.56 (3H, s), 2.84 (1H, qq, J=6.6 and 6.4Hz), 2.93 (3H, s), 6.15 (1H, broad s), 7.06 (2H, d, J= 8.4Hz), 7.33 (2H, d, J= 8.4Hz).

[0166] Example of reference It compounded according to the approach of the 311-(2-methoxy - 3, 4, 6-trimethyl phenyl)-1-(4-pentyl phenyl)-2-methyl propanol above. Yield 75.4%. Melting point 55 to 56 degree C (hexane). NMR (CDCl3) delta 0.85 (3H, t, J= 6.2Hz), 0.90 (3H, d, J= 6.6Hz) 1.03 (3H, d, J= 6.6Hz), 1.28 (4H, m) 1.56 (2H, quintet, J= 6.8Hz), 2.08 (3H, s), 2.18 (3H, s), 2.54 (2H, t, J= 7.5Hz), 2.55 (3H, s), 2.84 (1H, septet, J= 6.6Hz), 2.92 (3H, s), 6.15 (1H, broad s), 6.75 (1H, s), 7.07 (2H, d, J= 8.0Hz), 7.34 (2H, d, J= 8.0Hz).

[0167] Example of reference It compounded according to the approach of the 321-(4-isopropyl phenyl)-1-(2-methoxy - 3, 4, 6-trimethyl phenyl)-2-methyl propanol above. Yield 65.1%. Oily. NMR (CDCl3) delta 0.91 (3H, d, J= 6.6Hz), 1.02 (3H, d, J= 6.6Hz) 1.20 (6H, d, J= 7.0Hz), 2.08 (3H, s), 2.17 (3H, s), 2.54 (3H, s), 2.84 (1H, septet, J= 6.6Hz) 2.93 (3H, s), 2.96 (1H, septet, J= 7.0Hz), 6.16 (1H, broad s), 6.74 (1H, s), 7.10 (2H, d, J= 8.4Hz), 7.90 (2H, d, J= 8.4Hz).

[0168] Example of reference It compounded according to the approach of the 331-(2-methoxy -

3, 4, 6-trimethyl phenyl)-1-(3-pyridyl)-2-methyl propanol above. Yield 68.9%. Oily. NMR (CDCl3) delta 0.93 (3H, d, J= 6.6Hz), 1.03 (3H, d, J= 6.6Hz), 2.09 (3H, s), 2.19 (3H, s), 2.51 (3H, s) 2.90 (1H, septet, J= 6.6Hz), 3.05 (3H, s), 6.29 (1H, broad s), 6.76 (1H, s), 7.22 (1H, dd, J=4.8Hz and 8.0Hz), 7.79 (1H, dt, J=2.0Hz and 8.0Hz), 8.43 (1H, dd, J=2.0Hz and 4.8Hz), 8.70 (1H, d, J= 2.0Hz).

[0169] Example of reference It compounded according to the approach of the 341-(2-methoxy - 3, 4, 6-TORIMECHIRU)-1-(4-dimethylamino phenyl)-2-methyl propanol above. Yield 59.1%. Melting point 95 to 97 degree C (hexane). NMR (CDCl3) delta 0.93 (3H, d, J= 6.6Hz), 1.00 (3H, d, J= 6.4Hz), 2.08 (3H, s), 2.18 (3H, s), 2.53 (3H, s) 2.82 (1H, qq, J=6.4Hz and 6.6Hz), 2.90 (6H, s), 2.99 (3H, s), 6.12 (1H, broad s), 6.66 (2H, d, J= 9.0Hz), 6.74 (1H, s), 7.28 (2H, d, J= 9.0Hz).

[0170] Example of reference It compounded according to the approach of the 353-(2-methoxy - 3, 4, 6-trimethyl phenyl)-2 and 4-dimethyl pentane-3-all above. Yield 11.6%. Oily. NMR (CDCl3) delta 0.78 (6H, d, J= 6.6Hz), 1.03 (6H, d, J= 6.6Hz), 2.15 (3H, s), 2.19 (3H, s), 2.42 (3H, s), 2.45 (2H, septet, J= 6.6Hz), 3.73 (3H, s), 6.75 (1H, s), 6.88 (1H, s).

[0171] Example of reference 365-acetylamino [It compounded according to the approach of 3.] - 2, 2, 6, 7-tetramethyl - 2, 3-dihydrobenzofuran example Yield 71.9%. Melting point 163 to 164 degree C (ethanol).
NMR (CDCl3) delta 1.45 (6H, s), 2.10 (3H, s), 2.11 (3H, s), 2.17 (3H, s), 2.98 (2H, s), 7.00 (1H, s), 7.33 (1H, broad s).

[0172] Example of reference 375-acetylamino - 2, 2, 4, 7-tetramethyl - It compounded according to the approach of the 2 and 3-dihydrobenzofuran above. Yield 67.3%. Melting point 161 to 162 degree C (isopropyl ether).
NMR (CDCl3) delta 1.47 (6H, s), 2.06 (3H, s), 2.13 (3H, s), 2.14 (3H, s), 2.93 (2H, s), 6.81 (1H, broad s), 6.95 (1H, s).

[0173] Example of reference 385-amino - 2, 2, 4, 6-tetramethyl - It compounded according to the approach of the 2 and 3-dihydrobenzofuran hydrochloride above. Yield 43.0%. Melting point: 215 to 217 degree C (isopropanol). NMR (DMSO-d6) delta 1.40 (6H, s), 2.22 (3H, s), 2.29 (3H, s), 2.94 (2H, s), 6.49 (1H, s), 9.58 (2H, broad s).

[0174] Example of reference 395-amino - 2, 2, 6, 7-tetramethyl - It compounded according to the approach of the 2 and 3-dihydrobenzofuran hydrochloride above. Yield 38.7%. Melting point 235 to 238 degree C (ethanol).
NMR delta (CDCl3) 1.45 (6H, s), 2.13 (3H, s), 2.40 (3H, s), 2.97 (2H, s), 7.27 (2H, s), 10.23 (2H, broad s).

[0175] example of reference 402, 2, 4, 6, the 7-pentamethyl-3-phenyl -2, and 3-dihydrobenzofuran 1-(2-methoxy - 3, 4, 6-trimethyl phenyl)-1-phenyl-2-methyl propanol (3.1g, 10.4mmol) are suspended in a hydrobromic acid (20ml) 48% -- heating reflux was carried out for 18 hours. Isopropyl ether extracts a product, Rinsing, It condensed after desiccation. Residue is crystallized from ethanol, 2.43g (yield 87.8%) of specified substance was obtained. Melting point 86 to 87 degree C. NMR (CDCl3) delta 1.02 (3H, s), 1.51 (3H, s), 1.84 (3H, s), 2.15 (3H, s), 2.24 (3H, s), 4.13 (1H, s), 6.49 (1H, s), 6.70-7.40 (5H, m).

[0176] Example of reference It compounded according to 413-(4-fluoro phenyl)-2, 2, 4 and 6, 7-pentamethyl -2, and the approach of the 3-dihydrobenzofuran above. Yield 83.5%. Melting point 109 to 110 degree C (methanol). NMR (CDCl3) delta 1.02 (3H, s), 1, 49 (3H, s), 1.83 (3H, s), 2.14 (3H, s), 2.24 (3H, s), 4.10 (1H, s), 6.49 (1H, s), 6.60-7.20 (4H, m).

[0177] Example of reference It compounded according to the approach of the 422, 2, 4, 6, 7-pentamethyl-3-(4-methylphenyl)-2, and 3-dihydrobenzofuran above. Yield 87.7%. Melting point 117 to 118 degree C (methanol). NMR (CDCl3) delta 1.02 (3H, s), 1.50 (3H, s), 1.85 (3H, s), 2.15 (3H, s), 2.24 (3H, s), 2.31 (3H, s), 4.10 (1H, s), 6.49 (1H, s), 6.50-7.20 (4H, m).

[0178] Example of reference It compounded according to the approach of the 432, 2, 4, 6, 7-pentamethyl-3-(4-propyl phenyl)-2, and 3-dihydrobenzofuran above. Yield 84.9%. Melting point 69 to 70 degree C (methanol). NMR (CDCl3) delta 0.90 (3H, t, J= 7.2Hz), 1.02 (3H, s), 1.50 (3H, s), 1.61 (2H, sextet, J= 8.0Hz), 1.84 (3H, s), 2.15 (3H, s), 2.24 (3H, s), 2.55 (2H, t, J= 8.0Hz), 4.10 (1H, s), 6.49 (1H, s), 6.60-7.20 (4H, m).

[0179] Example of reference It compounded according to the approach of the 442, 2, 4, 6, 7-pentamethyl-3-(4-pentyl phenyl)-2, and 3-dihydrobenzofuran above. Yield 70.7%. Oily. NMR

(CDCl3) delta 0.88 (3H, t, J= 4.6Hz), 1.03 (3H, s), 1.30 (4H, m), 1.50 (3H, s), 1.56 (2H, m), 1.85 (3H, s), 2.15 (3H, s), 2.24 (3H, s), 2.56 (2H, t, J= 8.0Hz), 4.10 (1H, s), 6.45 (1H, s), 6.60-7.20 (4H, m).

[0180] Example of reference It compounded according to 453-(4-isopropyl phenyl)-2, 2, 4 and 6, 7-pentamethyl -2, and the approach of the 3-dihydrobenzofuran above. Yield 65.1%. Oily. NMR (CDCl3) delta 1.02 (3H, s) 1.21 (6H, d, J= 7.0Hz), 1.49 (3H, s), 1.84 (3H, s), 2.14 (3H, s), 2.24 (3H, s), 2.95 (1H, septet, J= 7.0Hz), 4.09 (1H, s), 6.48 (1H, s), 6.70-7.20 (4H, m).

[0181] Example of reference It compounded according to the approach of the 462, 2, 4, 6, 7-pentamethyl-3-(3-pyridyl)-2, and 3-dihydrobenzofuran above. Yield 77.1%. Oily. NMR (CDCl3) delta 1.05 (3H, s), 1.53 (3H, s), 1.84 (3H, s), 2.14 (3H, s), 2.24 (3H, s), 4.14 (1H, s), 6.50 (1H, s), 7.18 (2H, m), 8.35 (1H, m), 8.48 (1H, t, J= 3.2Hz).

[0182] Example of reference It compounded according to the approach of the 472, 2, 4, 6, 7-pentamethyl-3-(4-dimethylamino phenyl)-2, and 3-dihydrobenzofuran above. Yield 88.1%. Melting point 124 to 125 degree C (methanol). NMR (CDCl3) delta 1.03 (3H, s), 1.48 (3H, s), 1.85 (3H, s), 2.14 (3H, s), 2.23 (3H, s), 2.91 (6H, s), 4.04 (1H, s), 6.47 (1H, s), 6.55-7.00 (4H, m).

[0183] Example of reference It compounded according to 483-(4-isopropyl)-2, 2, 4 and 6, 7-pentamethyl -2, and the approach of the 3-dihydrobenzofuran above. Yield 88.2%. Oily. NMR (CDCl3) delta 0.73 (3H, d, J= 6.8Hz), 0.98 (3H, d, J= 7.2Hz), 1.21 (3H, s), 1.57 (3H, s), 2.06 (3H, s), 2.10 (1H, m), 2.20 (3H, s), 2.22 (3H, s), 2.73 (1H, d, J= 2.8Hz), 6.49 (1H, s).

[0184] Example of reference 492, 2, 4, 5, 6-pentamethyl-7-nitro -The mixed liquor of a 2 and 3-dihydrobenzofuran acetic anhydride (5ml) and an acetic acid (5ml) is cooled, The nitric acid (5ml) was added carefully with scrambling. Next, the acetic-anhydride (5ml) solution of 2, 2, 4, 5, 6-pentamethyl -2, and 3-dihydrobenzofuran (2.9g, 13.9mmol) was dropped, and was stirred for 30 minutes. Reaction mixture is poured out into iced water, Ethyl acetate extracted the product. Saturation sodium-hydrogencarbonate water washes an extract, It condensed after desiccation. A silica gel column chromatography (hexane-isopropyl ether and 9:1) refines residue, It was made to crystallize from a methanol and 0.35g (yield 9.8%) of specified substance was obtained. Melting point 100 to 101 degree C. NMR (CDCl3) delta 1.51 (6H, s), 2.14 (3H, s), 2.17 (3H, s), 2.24 (3H, s), 2.99 (2H, s).

[0185] Example of reference The mixed liquor of 502, 2, 4, 6, the 7-pentamethyl-5-nitro-3-phenyl -2, a 3-dihydrobenzofuran acetic anhydride (3ml), and an acetic acid (3ml) is cooled, The nitric acid (3ml) was added carefully with scrambling. Next, the acetic-anhydride (3ml) solution of 2, 2, 4, 6, the 7-pentamethyl-3-phenyl -2, and 3-dihydrobenzofuran (3.7g, 13.9mmol) was dropped, and was stirred for 30 minutes. Reaction mixture is poured out into iced water, Ethyl acetate extracted the product. Saturation sodium-hydrogencarbonate water washes an extract, It condensed after desiccation. A silica gel column chromatography (hexane-isopropyl ether and 9:1) refines residue, It was made to crystallize from a methanol and 2.08g (yield 48.1%) of specified substance was obtained. Melting point 155 to 156 degree C. NMR (CDCl3) delta 1.04 (3H, s), 1.52 (3H, s), 1.83 (3H, s), 2.18 (3H, s), 2.20 (3H, s), 4.15 (1H, s), 6.85 (2H, m), 7.26 (3H, m).

[0186] Example of reference 513-(4-fluoro phenyl)-2, 2, 4 and 6, 7-pentamethyl-5-nitro -It compounded according to the approach of the 2 and 3-dihydrobenzofuran above. Yield 66.3%. Melting point 94 to 95 degree C (methanol). NMR (CDCl3) delta 1.04 (3H, s), 1.50 (3H, s), 1.84 (3H, s), 2.18 (3H, s), 2.20 (3H, s), 4.14 (1H, s), 6.50-7.20 (4H, m).

[0187] Example of reference 522, 2, 4, 6, 7-pentamethyl-3-(4-methylphenyl)-5-nitro -It compounded according to the approach of the 2 and 3-dihydrobenzofuran above. Yield 56.0%. Oily. NMR (CDCl3) delta 1.05 (3H, s), 1.50 (3H, s), 1.84 (3H, s), 2.18 (3H, s), 2.20 (3H, s), 2.32 (3H, s), 4.11 (1H, s), 6.50-7.20 (4H, m).

[0188] Example of reference It compounded according to the approach of the 532, 2, 4, 6, 7-pentamethyl-5-nitro-3-(4-propyl phenyl)-2, and 3-dihydrobenzofuran above. Yield 65.8%. Oily. NMR (CDCl3) delta 0.91 (3H, t, J= 7.4Hz), 1.04 (3H, s), 1.50 (3H, s), 1.61 (2H, sextet, J= 7.4Hz), 1.84 (3H, s), 2.18 (3H, s), 2.20 (3H, s), 2.55 (2H, t, J= 7.4Hz), 4.12 (1H, s), 6.50-7.20 (4H, m).

[0189] Example of reference It compounded according to the approach of the 542, 2, 4, 6, 7-pentamethyl-5-nitro-3-(4-pentyl phenyl)-2, and 3-dihydrobenzofuran above. Yield 76.4%. Oily. NMR (CDCl3) delta 0.89 (3H, t, J= 6.6Hz), 1.04 (3H, s), 1.30 (4H, m), 1.50 (3H, s), 1.59 (2H, m), 1.84 (3H, s), 2.18 (3H, s), 2.20 (3H, s), 2.56 (2H, t, J= 7.8Hz), 4.11 (1H, s), 5.50-7.20 (4H, m).

[0190] Example of reference 553-(4-isopropyl phenyl)-2, 2, 4 and 6, 7-pentamethyl-5-nitro -It compounded according to the approach of the 2 and 3-dihydrobenzofuran above. Yield 48.0%. Melting point 109 to 110 degree C (methanol). NMR (CDCl3) delta 1.04 (3H, s), 1.22 (6H, d, J= 6.8Hz), 1.50 (3H, s), 1.84 (3H, s), 2.18 (3H, s), 2.20 (3H, s), 2.87 (1H, septet, J= 6.8Hz), 4.12 (1H, s), 6.60-7.20 (4H, m).
[0191] Example of reference It compounded according to the approach of the 562, 2, 4, 6, 7-pentamethyl-5-nitro-3-(3-pyridyl)-2, and 3-dihydrobenzofuran above. Yield 60.7%. Oily. NMR (CDCl3) delta 1.07 (3H, s), 1.54 (3H, s), 1.84 (3H, s), 2.19 (3H, s), 2.21 (3H, s), 4.18 (1H, s), 7.05-7.35 (2H, m), 8.25-8.60(2H, m). [0192] Example of reference 572, 2, 4, 6, 7-pentamethyl-3-(4-dimethylamino-3-nitrophenyl)-5-nitro -It compounded according to the approach of the 2 and 3-dihydrobenzofuran above. Yield 24.2%. Oily. NMR (CDCl3) delta 1.13 (3H, s), 1.51 (3H, s), 1.91 (3H, s), 2.19 (3H, s), 2.21 (3H, s), 2.81 (6H, s), 4.12 (1H, s), 7.00-7.80 (3H, m).
[0193] Example of reference 583-isopropyl - 2, 2, 4, 6, 7-pentamethyl-5-nitro -It compounded according to the approach of the 2 and 3-dihydrobenzofuran above. Yield 62.0%. Oily. NMR (CDCl3) delta 0.72 (3H, d, J= 7.0Hz), 0.98 (3H, d, J= 7.2Hz), 1.23 (3H, s), 1.59 (3H, s), 2.09 (1H, m), 2.10 (3H, s), 2.16 (3H, s), 2.21 (3H, s), 2.78 (1H, d, J= 2.8Hz).
[0194] Example of reference It compounded according to 592, 4, 6, 7-tetramethyl-5-nitro-2-piperidinomethyl -2, and the approach of the 3-dihydrobenzofuran above. Yield 62.8%. Oily. NMR (CDCl3) delta 1.30-1.60 (6H, m), 1.42 (3H, s), 2.08 (3H, s), 2.14 (6H, s), 2.50 (6H, m), 2.78 (1H, d, J= 15.6Hz), 3.18 (1H, d, J= 15.6Hz).
[0195] Example of reference 602, 4, 6, 7-tetramethyl-2-morpholino methyl-5-nitro -It compounded according to the approach of the 2 and 3-dihydrobenzofuran above. Yield 59.0%. Oily. NMR (CDCl3) delta 1.44 (3H, s), 2.07 (3H, s), 2.15 (6H, s), 2.57 (6H, m), 2.80 (1H, d, J= 15.6Hz), 3.21 (1H, d, J= 15.6Hz), 3.66 (4H, t, J= 4.4Hz).
[0196] Example of reference 612, 4, 6, 7-tetramethyl-2-[2-(dimethylamino) ethyl]-5-nitro -It compounded according to the approach of the 2 and 3-dihydrobenzofuran above. Yield 53.0%. Oily. NMR (CDCl3) delta 1.44 (3H, s), 1.62 (2H, m), 2.10 (3H, s), 2.13 (3H, s), 2.15 (3H, s), 2.24 (6H, s), 2.40 (2H, m), 2.87 (1H, d, J= 15.6Hz), 3.06 (1H, d, J= 15.6Hz).
[0197] Example of reference It compounded according to the approach of the 622, 4, 6, 7-tetramethyl-5-nitro-2-(2-piperidino ethyl)-2, and 3-dihydrobenzofuran above. Yield 46.3%. Melting point 247 to 250 degree C. NMR (CDCl3) delta 1.50 (3H, s) 1.90 (2H, m), 2.08 (3H, s), 2.13 (3H, s), 2.14 (3H, s), 2.18 (4H, m), 2.40 (2H, m), 2.64 (2H, m), 2.97 (1H, d, J= 15.6Hz), 3.07 (2H, m), 3.17 (1H, d, J= 15.6Hz), 3.55 (2H, m).
[0198] example of reference 632, 2, 4, 5, 6-pentamethyl -2, the 3-dihydrobenzofurans 3 and 4, a 5-trimethyl phenol (5.0g, 36.7mmol), and 2-methyl-2-propenol (3.2g, 44.0mmol) are added into a formic acid (50ml) -- heating reflux was carried out for 3 hours. Reaction mixture is diluted with isopropyl ether, Water and saturation sodium-hydrogencarbonate water wash, It condensed after desiccation. A silica gel column chromatography (hexane-isopropyl ether and 97:3) refines residue, 2.9g (41.5%) of specified substance was obtained. Oily. NMR (CDCl3) delta 1.45 (6H, s), 2.09 (3H, s), 2.14 (3H, s), 2.23 (3H, s), 2.93 (2H, s), 6.44 (1H, s).
[0199] Example of reference 645-BUROMO-2-bromomethyl - 2, 4, 6, 7-tetramethyl - It compounded according to the approach of the 2 and 3-dihydrobenzofuran example 29. Yield 67.7%. Melting point 60 to 61 degree C (methanol). NMR (CDCl3) delta 1.61 (3H, s), 2.15 (3H, s), 2.27 (3H, s), 2.35 (3H, s), 2.67 (1H, d, J= 15.6Hz), 3.33 (1H, d, J= 15.6Hz), 3.51 (2H, s).
[0200] example of reference 652-bromomethyl [- Ethanol of 2 and 3-dihydrobenzofuran (12.4g, 35.6mmol)] - 2, 4, 6, 7-tetramethyl - 2 and 3-dihydrobenzofuran 5-BUROMO-2-bromomethyl - 2, 4, 6, 7-tetramethyl (100ml) Triethylamine (5.0ml, 35.6mmol) is added to a solution, and it is 5%-palladium carbon (5g) top, The catalytic hydrogenation decomposition reaction was performed under the hydrogen ambient atmosphere. After reaction termination, A catalyst is ****(ed), The filtrate was condensed. Residue is melted to isopropyl ether, Rinsing, The solvent after desiccation was distilled off. Residue was crystallized from the methanol and 8.84g (yield 92.2%) of specified substance was obtained. Melting point 39 to 40 degree C. NMR (CDCl3) delta 1.63 (3H, s) 2.08 (3H, s), 2.17 (3H, s), 2.21 (3H, s), 2.92 (1H, d, J= 15.8Hz), 3.26 (1H, d, J= 15.8Hz), 3.48 (1H, d, J= 15.6Hz), 3.58 (1H, d, J= 15.6Hz), 6.53 (1H, s).

[0201] Example of reference It compounded according to the approach of 662, 4, 6, 7-tetramethyl-2-piperidinomethyl -2, and the 3-dihydrobenzofuran example 57. Yield 81.6%. Oily. NMR (CDCl3) delta 1.30-1.60 (6H, m), 1.44 (3H, s), 2.05 (3H, s), 2.15 (3H, s) and 2.19 (3H, s), 2.40-2.65 (6H, m), 2.76 (1H, d, J= 15.2Hz), 3.06 (1H, d, J= 15.2Hz), 6.47 (1H, s).
[0202] Example of reference It compounded according to 672, 4, 6, the 7-tetramethyl-2-morpholino methyl -2, and the approach of the 3-dihydrobenzofuran above. Yield 99.8%. Oily. NMR (CDCl3) delta 1.44 (3H, s), 2.04 (3H, s), 2.15 (3H, s), 2.19 (3H, s), 2.40-2.70 (6H, m), 2.79 (1H, d, J= 15.4Hz), 3.08 (1H, d, J= 15.4Hz), 3.67 (4H, t, J= 4.6Hz), 6.48 (1H, s).
[0203] Example of reference 682-cyano methyl [- 2, 4, 6, 7-tetramethyl / - 2 and 3-dihydrobenzofuran (6.5g, 18.6mmol) is melted to dimethyl sulfoxide (30ml), / The sodium cyanide (1.43g, 88mmol) was added, and it stirred at 80 degrees C for 18 hours.] - 2, 4, 6, 7-tetramethyl - 2 and 3-dihydrobenzofuran 2-bromomethyl Reaction mixture is diluted with water, Ethyl acetate extracted the product. It is rinsing about an extract, It condenses after desiccation, The silica gel column chromatography (hexane-isopropyl ether and 2:1) refined residue. The obtained rough crystal was ******ed from the methanol and 4.1g (yield 79.7%) of specified substance was obtained. Melting point 58 to 59 degree C. NMR (CDCl3) delta 1.66 (3H, s) 2.07 (3H, s), 2.16 (3H, s), 2.20 (3H, s), 2.68 (1H, d, J= 10.8Hz), 2.75 (1H, d, J= 10.8Hz), 3.00 (1H, d, J= 15.8Hz), 3.12 (1H, d, J= 15.8Hz), 6.54 (1H, s).
[0204] Example of reference 692, 4, 6, 7-tetramethyl [- In 2 and the methanol (30ml) solution of 3-dihydrobenzofuran (6.9g, 32.1mmol) / The water (30ml) solution of a sodium hydroxide (12.0g, 300mmol) was added, and heating reflux was carried out for 18 hours.] - 2 3-dihydrobenzofuran-2-IRU acetic-acid 2-cyano methyl - 2, 4, 6, 7-tetramethyl Reaction mixture is taken as the acescence with 6N-hydrochloric acid, Ethyl acetate extracted the product. It is rinsing about an extract, It condenses after desiccation, Residue was crystallized from the ethyl-acetate-hexane and 6.0g (yield 79.9%) of specified substance was obtained. The 139 to 140 degree C melting point. NMR (DMSO-d6) delta 1.61 (3H, s) 2.07 (3H, s), 2.16 (3H, s), 2.21 (3H, s), 2.78 (1H, d, J= 10.8Hz), 2.85 (1H, d, J= 10.8Hz), 2.97 (1H, d, J= 15.4Hz), 3.21 (1H, d, J= 15.4Hz), 6.52 (1H, s), 8.50 (1H, broad s).
[0205] example of reference 70 Ns, N-dimethyl [Dimethylformamide of an acetic acid (3.0g, 12.8mmol)] - 2, 4, 6, 7-tetramethyl - 2 and 3-dihydrobenzofuran-2-ilacetamide 2, 4, and 6, 7-tetramethyl - 2 and 3-dihydrobenzofuran-2-IRU (30ml) It is 1-hydroxy-1H-benzotriazol to a solution. One hydrate (HOBt) (2.1g, 14.1mmol) and a 1-ethyl-3-(3-dimethylaminopropyl) carbodiimide hydrochloride (WSC) (3.7g, 19.2mmol) are added. It stirred at room temperature for 1 hour. Next, a dimethylamine water solution (3ml) is added 50%, It stirred for 30 more minutes. Reaction mixture is diluted with water, Ethyl acetate extracted the product. It is rinsing about an extract, It condenses after desiccation, The silica gel column chromatography (isopropyl ether) refined residue, and 3.1g (yield 92.6%) of specified substance was obtained. Oily. NMR (CDCl3) delta 1.59 (3H, s) 2.07 (3H, s), 2.14 (3H, s), 2.20 (3H, s), 2.77 (1H, d, J= 15.0Hz), 2.88 (1H, d, J= 15.0Hz), 2.94 (3H, s), 3.00 (1H, d, J= 15.8Hz), 3.03 (3H, s), 3.27 (1H, d, J= 15.8Hz), 6.50 (1H, s).
[0206] Example of reference It compounded according to the approach of the 71 (2, 4, 6, 7-tetramethyl - 2 and 3-dihydrobenzofuran-2-IRU) acetyl-1-piperidine above. Yield 90.7%. Oily. NMR (CDCl3) delta 1.55 (3H, s) 1.60 (6H, m), 2.06 (3H, s), 2.13 (3H, s), 2.19 (3H, s), 2.78 (1H, d, J= 14.8Hz), 2.90 (1H, d, J= 14.8Hz), 2.97 (1H, d, J= 15.8Hz), 3.24 (1H, d, J= 15.8Hz), and 3.40- 3.60 (4H, m) and 6.50 (1H, s).
[0207] Example of reference The 722, 4, 6, 7-tetramethyl-2-[2-(dimethylamino) ethyl]-2, and 3-dihydrobenzofuran N, N-dimethyl-2.4.6.7-tetramethyl - 2 and 3-dihydrobenzofuran-2-ilacetamide (3.1g, 11.9mmol) is melted to a tetrahydrofuran (50ml), The lithium aluminum hydride (0.45g) was added little by little, cooling. After stirring reaction mixture at a room temperature for 30 minutes It poured into iced water., Ethyl acetate extracts a product, An extract is the rinsing desiccation back, It condensed. A silica gel column chromatography (a chloroform-methanol and 95:5) refines residue, 2.2g (yield 81.6%) of specified substance was obtained. Oily. NMR (CDCl3) delta 1.42 (3H, s) 1.90 (2H, m), 2.06 (3H, s), 2.12 (3H, s), 2.19 (3H, s), 2.23 (6H, s), 2.40 (2H, m), 2.82 (1H, d, J= 15.4Hz), 3.00 (1H, d, J= 15.4Hz), 6.47 (1H, s).
[0208] Example of reference It compounded according to the approach of the 732, 4, 6, 7-

tetramethyl-2-(2-piperidino ethyl)-2, and 3-dihydrobenzofuran above. Yield 74.9%. Oily. NMR (CDCl3) delta 1.42 (3H, s) 1.30-1.60 (6H, m), 1.90 (2H, m), 2.05 (3H, s), 2.12 (3H, s), 2.21 (3H, s), 2.40-2.60 (6H, m), 2.82 (1H, d, J= 15.8Hz), 3.00 (1H, d, J= 15.8Hz), 6.47 (1H, s).

[0209] example of reference 744-(4-chloro FENIRUMINO)- the titanium tetrachloride (2.42ml, 22.1mmol) was dropped at the 1,2-dichloroethane (40ml) solution of a 3, 5, 6-trimethyl-2-(2-methyl-2-propenyl)-2, and 5-cyclohexadiene-1-on-pyridine (7.13ml, 88.2mmol), and the heating reflux of the reaction mixture after dropping termination was carried out for 20 minutes under the argon ambient atmosphere. After cooling reaction mixture, the 1,2-dichloroethane (20ml) solution of 3, 5, the 6-trimethyl-2-2-methyl-2-propenyl-1, 4-benzoquinone (3.00g, 14.7mmol), and p-chloroaniline (5.62g, 44.1mmol) was added to this; and mixture was agitated for 45 minutes at 90 degrees C under the argon ambient atmosphere. After cooling reaction mixture, cerite filtration was carried out, and the filtrate was dried and condensed after washing with saturation brine. The silica gel column chromatography (hexane-ethyl acetate, 93:7) refined residue, and 4.43g (yield 96.0%) of specified substance was obtained. Oily.

NMR (CDCl3) delta 1.53-2.20 (12H, m), 3.21 (2H, s), 4.51 (1H, s), 4.74 (1H, s), 6.68 (2H, d, J= 8.8Hz), 7.30 (2H, d, J= 8.8Hz).

[0210] example of reference 754-(4-methoxyphenylimino)- 3, 5, and 6-trimethyl-2- (2-methyl-2-propenyl) It compounded according to the same approach as the example 74 of -2 and 5-cyclohexadiene-1-ON reference. Yield 19.1%. Oily.

NMR (CDCl3) delta 1.50- 1.60 (3H, m) and 1.77 (3H, broad s) -- 1.95- 2.03 (3H, m) and 2.25 (3H, broad s) -- 3.16- 3.25 (2H, m), 3.82 (3H, s), 4.46-4.58 (1H, m), and 4.74 (1H, broad s), 6.72 (2H, d, J= 9.0Hz) and 6.88 (2H, d, J= 9.0Hz).

[0211] example of reference 764- (4-chlorophenylamino) - 3, 5, and 6-trimethyl-2-(2-methyl-2-propenyl) phenol 4-(4-chlorophenylimino)- 3, 5, 6-trimethyl-2-(2-methyl-2-propenyl)-2, and 5-cyclohexadiene-1-ON (4.40g) The water (50ml) solution of sodium-hydrosulfite sodium (24.4g, 0.14 mols) was added to the tetrahydrofuran (20ml) solution of 14.0mmol, and it agitated for 30 minutes at the room temperature. After isolating an organic layer preparatively, ethyl acetate extracted the water layer. After having doubled the extract and the organic layer, rinsing this and drying, the solvent was distilled off under reduced pressure. The silica gel column chromatography (hexane-ethyl acetate, 95:5) refined residue, and 4.30g (yield 97.2%) of specified substance was obtained. Oily. NMR (CDCl3) delta 1.80 (3H, s) 2.11 (3H, s), 2.12 (3H, s), 2.19 (3H, s), 3.40 (2H, s), 4.68 (1H, s), 4.87 (1H, s), 5.04 (1H, s), 5.14 (1H, broad s), 6.34 (2H, d, J= 8.8Hz), 7.06 (2H, d, J= 8.8Hz).

[0212] example of reference 774-(4-methoxy phenylamino)- 3, 5, and 6-trimethyl-2- (2-methyl-2-propenyl) It compounded according to the same approach as the example 74 of phenol reference. Yield 98.2%. Oily. NMR (CDCl3) delta 6.38 (2H, d, J= 8.8Hz) 1.80 (3H, s), 2.14 (6H, s), 2.19 (3H, s), 3.40 (2H, s), 3.73 (3H, s), 4.69 (1H, s), 4.85-5.05 (3H, m), 6.73 (2H, d, J= 8.8Hz).

[0213] Example of reference The titanium tetrachloride (2.58ml, 23.4mmol) was dropped at 783, 5, and the 1,2-dichloroethane (40ml) solution of a 6-trimethyl-2-(2-methyl-2-propenyl)-4-phenylamino phenol pyridine (7.60ml, 93.6mmol), and the heating reflux of the reaction mixture after dropping termination was carried out for 30 minutes under the argon ambient atmosphere. It is 3, 5, and 6-trimethyl to this after cooling reaction mixture. -2 -(2-methyl-2-propenyl)- The 1, 4-benzoquinone (2.40g, 11.7mmol) and the 1,2-dichloroethane (5ml) solution of an aniline (3.35ml, 35.1mmol) were added, and mixture was agitated at 90 degrees C under the argon ambient atmosphere for 2 hours. After cooling reaction mixture, cerite filtration was carried out and the filtrate was condensed under reduced pressure. The silica gel column chromatography (hexane-ethyl acetate, 98:2) refined residue. The water (30ml) solution of sodium-hydrosulfite sodium (12g, 69mmol) was added to the tetrahydrofuran (10ml) solution of the obtained compound, and it agitated for 30 minutes at the room temperature. After isolating an organic layer preparatively, ethyl acetate extracted the water layer. The extract and the organic layer were doubled and the solvent was distilled off for this under reduced pressure after rinsing and desiccation. The silica gel column chromatography (hexane-ethyl acetate and 95:5) refined residue, and 1.41g (yield 42.8%) of specified substance was obtained. Oily. NMR (CDCl3) delta 1.80 (3H, s) 2.14 (6H, s), 2.19 (3H, s), 3.41 (2H, s), 4.69 (1H, s), 4.87 (1H, s), 5.03(1H, s) 5.11, (1H,

broad s), 6.42 (2H, d, J= 7.4Hz), 6.68 (1H, t, J= 7.4Hz), 7.13 (2H, t, J= 7.4Hz).
[0214] The 5 weeks-old male Slc:ICR mouse of ten operation 1 groups of a drug to the action change by the administration in an example of trial 1 ferrous-chloride mouse spine subarachnoid cavity was used. After pouring in 5micro [of physiological sodium chloride solution] l / mouse which dissolved 50mM ferrous chloride into the subarachnoid cavity of the 1st sacral region of spinal cord from the 6th lumbar cord, behavior observation was performed from 15 minutes to 1 hour, and the score of action change was performed on the following criteria.
Score Zero action change: One normal: The membrum inferius and the hypogastrium are bit very often.
two points : a — sometimes it falls violently and a lower half of the body is bit with the surroundings.
b) The allergic reaction to an external stimulus is accepted and it becomes offensive. c) A tremor happens.
Either of three reactions is accepted above.
Three points : A clonic spasm is accepted.
Four points : A tonic convulsion is accepted. or one side or both sides — paralysis of a leg is accepted.
Five points : It dies.
The rate of control showed based on the mark evaluated by the above criteria. The test compound was administered orally in [ferrous chloride administration] 30 minutes. The average score and each rate of control when carrying out 100 mg/kg internal use of the compound [I], respectively are shown in Table 1.
[Table 1]

化合物 実施例No.	平均スコアー		抑制率 (%)
	100mg／kg 投与	生理食塩水 投与	
103	0.1	4.9	98.0
1	1.2	4.6	73.9
84	0.5	4.6	89.1
47	1.0	4.9	79.6
85	0.6	4.6	87.0

The above result shows that this invention compound is excellent in the depressant action of the central nervous system failure accompanying the peroxylipid generation by ferrous chloride.
[0215]
[Effect of the Invention] this invention compound [I] has peroxylipid generation depressant action (antioxidation operation), lipoxygenase and generation inhibition of HHT, or depressant action, as shown by said example of a trial, and it is useful as physic for the therapy of a circulatory system disease, inflammation, the allergosis, etc., or prevention.

[Translation done.]

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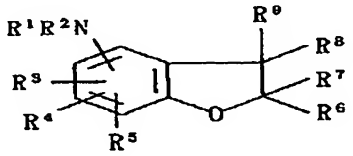
(71)出願人　000002934
武田薬品工業株式会社
大阪府大阪市中央区道修町四丁目１番１号
(72)発明者　青野　哲也
京都府長岡京市高台３丁目７番地の４
(72)発明者　大川　滋紀
大阪府高槻市真上町６丁目45番20号
(72)発明者　土居　孝行
大阪府和泉市鶴山台１丁目10番25号
(74)代理人　弁理士　青山　葆　（外１名）

(54)【発明の名称】　アミノクマラン誘導体

(57)【要約】　（修正有）
【構成】　一般式の化合物、その塩およびそれらの製造法、ならびにそれを有効成分とする過酸化脂質生成抑制剤。
【化１】

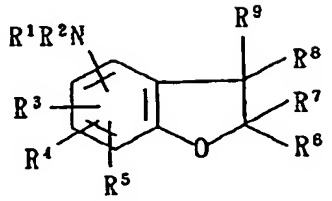


［式中、Ｒ¹およびＲ²は、Ｈ、アシル基、アルコキシカルボニル基、脂肪族基または芳香環基を、Ｒ³，Ｒ⁴およびＲ⁵は、（アシル化）水酸基、アミノ基、アルコキシ基または脂肪族基であるか、またはＲ³，Ｒ⁴およびＲ⁵のうち二つが炭素同素環を形成していてもよく、Ｒ⁶およびＲ⁷は、脂肪族基であり、しかも、Ｒ⁶およびＲ⁷のうち少なくとも一つはα位がメチレン基であり、Ｒ⁸およびＲ⁹は、水素原子またはそれぞれ脂肪族基または芳香環基を示す］

【効果】　過酸化脂質生成抑制作用ならびにリポキシゲナーゼおよびＨＨＴの生成阻害・抑制作用を有しており、循環器系疾患、炎症、アレルギー疾患等の治療・予防用医薬として有用である。

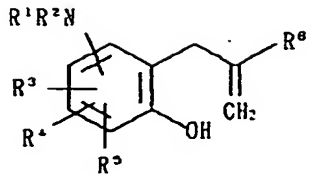
1

【特許請求の範囲】
【請求項１】　一般式
【化１】

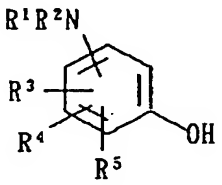


[式中、R^1およびR^2は、同一または異なって、水素原子、アシル基、アルコキシカルボニル基、それぞれ置換基を有していてもよい脂肪族基または芳香環基を、R^3、R^4およびR^5は、同一または異なって、アシル化されていてもよい水酸基、それぞれ置換基を有していてもよいアミノ基、アルコキシ基または脂肪族基であるか、またはR^3、R^4およびR^5のうち二つが置換基を有していてもよい炭素同素環を形成していてもよく、R^6およびR^7は、同一または異なって、置換基を有していてもよい脂肪族基であり、しかも、R^6およびR^7のうち少なくとも一つはα位がメチレン基であり、R^8およびR^9は、同一または異なって、水素原子またはそれぞれ置換基を有していてもよい脂肪族基または芳香環基を示す]で表わされる化合物またはその塩。
【請求項２】　R^6およびR^7が、ヒドロキシル；C_{1-3} アルコキシ；アラルキルオキシ；アリールオキシ；メルカプト；C_{1-3} アルキルチオ；C_{1-3} アルキルスルホニル；C_{1-3} アルキルスルフィニル；アラルキルチオ；アラルキルスルホニル；アラルキルスルフィニル；アリールチオ；アリールスルホニル；アリールスルフィニル；アミノ；C_{1-3} アルキル、アラルキル、アリールの１ないし２個で置換されたモノまたはジ置換アミノ；ハロゲン；エステル化カルボキシ；C_{2-3} アシル；C_{2-3} アシルオキシ；C_{2-3} アシルアミド；C_{2-5} アルコキシカルボニルアミノ；環状アミノ；カルボキシル；カルバモイルおよびフェニル（アミノ、モノまたはジC_{1-3} アルキルアミノ、ハロゲン、ニトロ、スルホ、シアノ、ヒドロキシ、カルボキシ、C_{1-5} アルキル、C_{1-3} アルコキシ、C_{2-5} アシルおよびC_{1-3} アルキルメルカプトから選ばれる１個以上の置換基で置換されていてもよい）から選ばれる１ないし２個の置換基で置換されていてもよい脂肪族基であり、しかも、R^6およびR^7のうち少なくとも１つはα位がメチレン基である請求項１記載の化合物またはその塩。
【請求項３】　一般式
【化２】

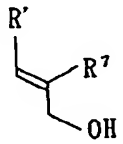
2



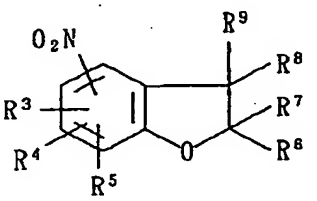
[式中、各記号は請求項１記載と同意義を示す]で表される化合物またはその塩を閉環反応に付し、さらに所望により、閉環反応生成物を脱保護反応、アシル化反応、水素添加反応、酸化反応、炭素鎖延長および置換基交換反応の単独あるいはその二以上を組み合わせた反応に付すことを特徴とする請求項１記載の化合物またはその塩の製造法。
【請求項４】　一般式
【化３】



[式中、各記号は請求項１記載と同意義を示す]で表される化合物またはその塩を一般式
【化４】



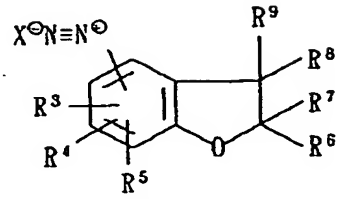
[式中、－CH_2R'は請求項１記載のR^6と対応した基を、R^7は請求項１記載と同意義を示す]で表される化合物と縮合反応に付し、さらに所望により、縮合反応生成物を脱保護反応、アシル化反応およびアルキル化反応の単独あるいはその二以上を組み合わせた反応に付すことを特徴とする請求項１記載の化合物またはその塩の製造法。
【請求項５】　一般式
【化５】



[式中、各記号は請求項１記載と同意義を示す]で表される化合物またはその塩を還元反応に付し、さらに所望により、還元反応生成物を脱保護反応、アシル化反応およびアルキル化反応の単独あるいはその二以上を組み合わせた反応に付すことを特徴とする請求項１記載の化合物またはその塩の製造法。

【請求項６】　一般式

【化６】



[式中、Ｘはハロゲン、ＨＳＯ４またはＮＯ３を、他の記号は請求項１記載と同意義を示す]で表される化合物またはその塩を還元反応に付し、さらに所望により、還元反応生成物を脱保護反応、アシル化反応およびアルキル化反応の単独あるいはその二以上を組み合わせた反応に付すことを特徴とする請求項１記載の化合物またはその塩の製造法。

【請求項７】　請求項１記載の化合物またはその塩を含有することを特徴とする過酸化脂質生成抑制剤。

【発明の詳細な説明】

【０００１】

【産業上の利用分野】本発明は、新規アミノクマラン誘導体またはその塩およびこれを有効成分とする医薬組成物に関する。さらに詳しくは、動脈硬化、肝疾患、脳血管障害等の種々の疾患の予防・治療剤として有用な新規過酸化脂質生成抑制作用を有する新規アミノクマラン誘導体またはその塩およびそれを有効成分とする過酸化脂質生成抑制剤に関する。

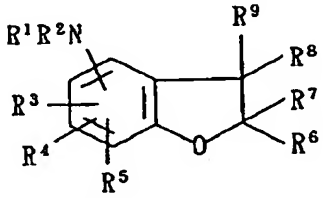
【０００２】

【従来の技術および発明が解決しようとする課題】体内での過酸化脂質の生成およびそれに付随したラジカル反応が、膜障害や酵素障害等を介して生体に種々の悪影響を及ぼすことが明らかになるにつれて、抗酸化・過酸化脂質生成抑制剤の医薬への応用が種々試みられる様になってきた。現在、医薬分野で用いられる過酸化脂質生成抑制剤は、主として、ビタミンＣやビタミンＥ等の天然抗酸化剤の誘導体およびフェノール誘導体である（福沢健治著、日本臨床４６巻、２２６９～２２７６頁（１９８８））が、作用が弱かったり、副作用があったり、実用的に必ずしも満足できるものではない。また、アミノクマラン誘導体としては従来、特開昭６０－１３２９７７号（用途：冠状脈管系の疾患の予防・治療剤として有用な２，２'－イミノビスエタノール誘導体の中間体）、特開昭６０－１６９４７３号（用途：鎮吐剤、抗精神病剤）、特開昭６２－２３４０８３号（用途：鎮吐剤、抗精神病剤）、特開昭６４－３８０９０号（用途：糖尿病およびその合併症ならびに高脂血症の治療薬）、特表平１－５０１２２６号（用途：鎮吐剤）および米国特許第４，７７２，７３０号（用途：ピラゾリン殺虫剤）が知られている。しかし、アミノクマランのベンゼン環に特定の置換基を４つ有し、かつアミノクマランの２位に置換基を有していてもよい脂肪族基を２つ有し、そのうち少なくとも１つはα位がメチレン基であるアミノクマラン誘導体は従来全く合成されていなかった。本発明の主たる目的は、優れた過酸化脂質生成抑制作用を有する新規化合物、工業的有利なその製造法およびそれを有効成分とする過酸化脂質生成抑制剤を提供することにある。

【０００３】

【課題を解決するための手段】本発明者らは前記課題を解決するために、数多くの新規化合物を合成し、それぞれについて抗酸化活性・過酸化脂質生成抑制作用を調べた。その結果、一般式[Ｉ]

【化７】



[式中、Ｒ１およびＲ２は、同一または異なって、水素原子、アシル基、アルコキシカルボニル基、それぞれ置換基を有していてもよい脂肪族基または芳香環基を、Ｒ３、Ｒ４およびＲ５は、同一または異なって、アシル化されていてもよい水酸基、それぞれ置換基を有していてもよいアミノ基、アルコキシ基または脂肪族基であるか、またはＲ３、Ｒ４およびＲ５のうち二つが置換基を有していてもよい炭素同素環を形成していてもよく、Ｒ６およびＲ７は、同一または異なって、置換基を有していてもよい脂肪族基であり、しかも、Ｒ６およびＲ７の少なくとも１つはα位がメチレン基であり、Ｒ８およびＲ９は、同一または異なって、水素原子またはそれぞれ置換基を有していてもよい脂肪族基または芳香環基を示す]で表わされる新規構造のアミノクマラン誘導体あるいはその塩の創製に成功するとともに、これらの新規化合物が強力な過酸化脂質生成抑制作用等医薬として有用な作用を有することを見出し、さらに検討を重ねて本発明を完成した。

【０００４】すなわち、本発明は前記一般式[Ｉ]で表わされる新規アミノクマラン誘導体、その塩およびそれを有効成分とする医薬組成物を提供するものである。

【０００５】一般式[Ｉ]において、Ｒ１およびＲ２で表わされるアシル基としては、カルボン酸アシル、スルホン酸アシル等が挙げられる。カルボン酸アシルとしては炭素数１～６のアシル基(例、ホルミル、アセチル、プロピオニル、ブチリル、イソブチリル、バレリル等)、スルホン酸アシル基としてはメタンスルホニル、エタンスルホニル、プロパンスルホニル等の炭素数１～３のアルキルスルホニル基やフェニルスルホニル基が挙げられる。Ｒ１およびＲ２で表わされるアルコキシカルボニル基としてはメトキシカルボニル基、エトキシカルボニル基等のアルコキシの炭素数１～５の低級アルコキシカルボニル基が挙げられる。

【０００６】R^1およびR^2で表わされる脂肪族基は飽和の基であっても、また不飽和の基であってもよく、例えば、アルキル基、アルケニル基、アルキニル基が挙げられる。該アルキル基は直鎖状、分枝状あるいは環状でもよい。これらアルキル基のうち、炭素数１～６程度の低級アルキル基が好適で、例えば、メチル、エチル、プロピル、i－プロピル、ブチル、i－ブチル、t－ブチル、ペンチル、ヘキシル、シクロプロピル、シクロブチル、シクロペンチル等が挙げられる。また、R^1およびR^2で表わされるアルケニル基としては、一般に炭素数２～６のものが好ましく、例えば、アリル、プロペニル、i－プロペニル、２－ブテニル、２，４－ブタジエニル、２－ペンテニル等が挙げられる。また、R^1およびR^2で表わされるアルキニル基としては一般に、炭素数２～６の基が好ましく、例えば、エチニル、２－プロピニル等が挙げられる。

【０００７】これらの脂肪族基が有していてもよい置換基としては特に限定するものではなく、通常医薬に用いられる基であればどのようなものでもよく、具体的には、例えば、ヒドロキシル；C_{1-3} アルコキシ(例えば、メトキシ、エトキシ、n－プロポキシまたはiso－プロポキシなど)；アラルキルオキシ（フェニル－C_{1-6} アルキルオキシまたはナフチル－C_{1-6} アルキルオキシ、例えば、ベンジルオキシ、フェネチルオキシなど）；アリールオキシ（例えば、フェニルオキシ、ナフチルオキシ、ピリジルオキシ、イミダゾリルオキシなど）；メルカプト；C_{1-3} アルキルチオ(例えば、メチルチオまたはエチルチオなど)；C_{1-3} アルキルスルホニル（例えば、メチルスルホニルまたはエチルスルホニルなど）；C_{1-3} アルキルスルフィニル（例えば、メチルスルフィニルまたはエチルスルフィニルなど）；アラルキルチオ（フェニル－C_{1-6} アルキルチオまたはナフチル－C_{1-6} アルキルチオ、例えば、ベンジルチオ、フェネチルチオなど）；アラルキルスルホニル（フェニル－C_{1-6} アルキルスルホニルまたはナフチル－C_{1-6} アルキルスルホニル、例えば、ベンジルスルホニル、フェネチルスルホニルなど）；アラルキルスルフィニル（フェニル－C_{1-6} アルキルスルフィニルまたはナフチル－C_{1-6} アルキルスルフィニル、例えばベンジルスルフィニル、フェネチルスルフィニルなど）；アリールチオ（例えば、フェニルチオ、ナフチルチオ、ピリジルチオ、イミダゾリルチオなど）；アリールスルホニル（例えば、フェニルスルホニル、ナフチルスルホニル、ピリジルスルホニルまたはイミダゾリルスルホニルなど）；アリールスルフィニル（例えば、フェニルスルフィニル、ナフチルスルフィニル、ピリジルスルフィニルまたはイミダゾリルスルフィニルなど）；アミノ；C_{1-3} アルキル、アラルキル（フェニル－C_{1-6} アルキルまたはナフチル－C_{1-6} アルキルなど）、アリール（フェニル、ナフチル、ピリジルまたはイミダゾリルなど）の１ないし２個で置換されたモノまたはジ置換アミノ(例えば、メチルアミノ、エチルアミノ、ジメチルアミノ、ベンジルアミノ、フェニルアミノ、ピリジルアミノなど)；ハロゲン（例えば、クロロまたはフルオロ）；エステル化カルボキシ［例えば、C_{2-5} アルコキシカルボニル(メトキシカルボニルまたはエトキシカルボニルなど)］；C_{2-3} アシル(例えば、アセチル、プロピオニルなど)；C_{2-3} アシルオキシ(例えば、アセトキシ、プロピオニルオキシなど)；C_{2-3} アシルアミド(例えば、アセトアミドなど)；C_{2-5} アルコキシカルボニルアミノ(例えば、メトキシカルボニルアミノまたはエトキシカルボニルアミノなど)；環状アミノ基(例えば、ピロリジノ、モルホリノ、ピペラジノなど)；カルボキシル基；カルバモイル基などが挙げられる。これらの置換基の数は１～２個が好ましい。

【０００８】R^1およびR^2で表わされる芳香環基としては、フェニル基が挙げられる。フェニル基上の置換基としては、例えば、アミノ基、炭素数１～３の低級アルキル基で置換されたモノまたはジアルキルアミノ基、ハロゲン、ニトロ、スルホ、シアノ、ヒドロキシ、カルボキシ、炭素数１～５の低級アルキル、炭素数１～３の低級アルコキシ、炭素数２～５のアシル基、炭素数１～３の低級アルキルメルカプト基などが挙げられる。置換基の数は特に限定するものではないが、好ましい置換基の数は１～３である。

【０００９】－NR^1R^2で表される基はクマランのベンゼン環上のいずれの位置に置換していてもよいが、好ましくは、クマランの５位に置換しているものがよい。R^1およびR^2は、一方が水素原子で、他方が水素原子、フェニル基または直鎖状、分枝状あるいは環状の炭素数１～６のアルキル基が好ましい。

【００１０】R^3、R^4およびR^5で表わされる水酸基がアシル化されている場合、そのアシル基としては、炭素数２～５の直鎖または分枝状のカルボン酸アシル基（例えば、アセチル、プロピオニル、ブチリル、イソブチリルなど）が挙げられる。R^3、R^4およびR^5で表わされるアミノ基が置換基を有する場合、その置換基としては、R^1およびR^2で表わされるそれぞれ置換基を有していてもよい脂肪族基または芳香環基が挙げられる。

【００１１】R^3、R^4およびR^5で表わされるアルコキシ基としては、炭素数１～６の直鎖状または分枝状のアルキル基、または環状のアルキル基からなるアルコキシ基が挙げられ、アルコキシ基が有する置換基としては、例えば、アミノ基、炭素数１～３の低級アルキル基で置換されたモノまたはジアルキルアミノ基、ハロゲン、ヒドロキシ、低級アルコキシ、低級アルキルメルカプト基などが挙げられる。

【００１２】R^3、R^4およびR^5で表わされる脂肪族基および脂肪族基が有していてもよい置換基はR^1およびR^2で表わされる脂肪族基に準ずる。

【００１３】また、R^3、R^4およびR^5のうちの二つ

は、置換基を有していてもよい炭素同素環を形成していてもよく、この場合、５または６員の炭素同素環が好ましい。その置換基としては、炭素数１～３のアルキル基、炭素数１～３のアルコキシ基、水酸基等が挙げられる。R^3、R^4およびR^5は、直鎖状、分枝状あるいは環状の炭素数１～６のアルキル基が好ましい。

【００１４】R^6およびR^7で表わされる脂肪族基はR^1およびR^2の場合と同じであり、R^6およびR^7で表わされる脂肪族基が有する置換基はR^1およびR^2で表わされる脂肪族基の置換基の他に、置換されていてもよい芳香環基が含まれる。置換されていてもよい芳香環基および置換基としては、R^1およびR^2で表わされる芳香環基および置換基が挙げられる。

【００１５】さらに、R^6およびR^7のうち少なくとも一つは、α－位がメチレン基である。すなわち、言い換えると、R^6およびR^7は、置換されていてもよい脂肪族基であって、少なくとも一つは式

$-CH_2R'$

［式中、R'は水素または$-CH_2$と共に置換されていてもよい脂肪族基を形成する基を示す］で表される基を示す。R'で表される$-CH_2$と共に置換されていてもよい脂肪族基を形成する基における脂肪族基およびその脂肪族基が有する置換基は、R^6およびR^7で表される基に準ずる。R^6およびR^7は、一方が直鎖状、分枝状あるいは環状の炭素数１～６のアルキル基で、他方がヘテロ原子（Ｎ、Ｓ、Ｏ）を１～５個有する基で置換されていてもよい直鎖状、分枝状あるいは環状の炭素数１～６のアルキル基またはアラルキル基（フェニル－C_{1-6} アルキルまたはナフチル－C_{1-6} アルキルが好ましく、例えば、ベンジル、フェネチルまたはフェニルプロピルなど）が好ましい。該ヘテロ原子を１～５個有する基としては例えば、C_{1-3} アルコキシ、アラルキルオキシ、アリールオキシ、C_{1-3} アルキルチオ、C_{1-3} アルキルスルホニル、C_{1-3} アルキルスルフィニル、アラルキルチオ、アルキルスルホニル、アラルキルスルフィニル、アリールチオ、アリールスルホニル、アリールスルフィニル、モノまたはジ置換アミノ（C_{1-3} アルキル、アラルキル、アリールの１ないし２個で置換されたアミノ）および環状アミノ基が挙げられる。

【００１６】R^8およびR^9で表わされる脂肪族基はR^6およびR^7の場合と同じであり、R^8およびR^9で表わされる芳香環基はR^1およびR^2の場合と同じである。R^8およびR^9は、一方が水素原子で、他方が水素原子、ハロゲンまたは直鎖状、分枝状あるいは環状の炭素数１～６のアルキル基で置換されていてもよいフェニル基または直鎖状、分枝状あるいは環状の炭素数１～６のアルキル基が好ましい。

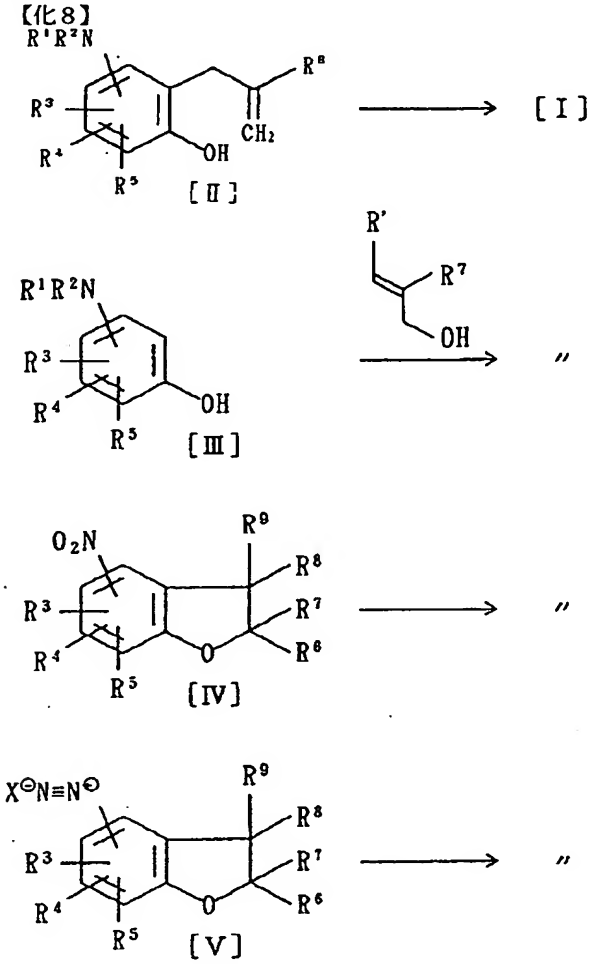
【００１７】なお、一般式［Ｉ］で示される化合物は、置換基の種類如何によっては立体異性体が生じるが、これら異性体単独のみならず、それらの混合物も本発明に含まれる。

【００１８】一般式［Ｉ］で表わされる化合物の塩としては、好ましくは、医薬上許容される塩であり、医薬上許容される塩の例としては、ハロゲン化水素酸(例、塩酸、臭化水素酸)、リン酸、硫酸などの無機酸や有機カルボン酸(例、シュウ酸、フタル酸、フマル酸、マレイン酸)、スルホン酸(例、メタンスルホン酸、ベンゼンスルホン酸)などの有機酸が挙げられる。また化合物［Ｉ］が置換基としてカルボキシル基等の酸性基を有する場合、アルカリ金属(例、ナトリウム、カリウム)またはアルカリ土類金属(例、マグネシウム)等との無機塩基塩および有機塩基(例、ジシクロヘキシルアミン、トリエチルアミン、２，６－ルチジン等のアミン類)との塩が挙げられる。以下、一般式［Ｉ］で表わされる化合物およびその塩を化合物［Ｉ］と総称する。

【００１９】本発明の化合物［Ｉ］は、例えば、反応式－１の方法により製造することができる。

反応式－１

【化８】



［式中、R^1、R^2、R^3、R^4、R^5、R^6、R^7、R^8、R^9は前記と同意義を、$-CH_2R'$は前記のR^6と対応した基を、Ｘはハロゲン、HSO_4またはNO_3を示す。］

【００２０】すなわち、化合物[Ｉ]は化合物[II]を、所望により酸の存在下、閉環させるか、ハロゲン分子を用いて、さらに所望により塩基の存在下、閉環して製造するか、または、過酸を用いて、さらに所望により塩基の存在下、閉環させて製造する。さらに所望により、脱保護反応、アシル化反応、水素添加反応、酸化反応、ビッティッヒ(Wittig)反応による炭素鎖延長および置換基交換反応を各々、単独あるいはその二以上を組み合わせて行うことにより合成することができる。また、化合物[Ｉ]は、フェノール[III]をアリルアルコール誘導体と、適当な酸触媒の存在下縮合させることにより、あるいは、ニトロ化合物[IV]やジアゾ化合物[V]を還元することによって製造し、さらに所望により、脱保護反応、アシル化反応およびアルキル化反応の単独あるいはその二以上を組み合わせた反応に付すことによっても合成することができる。上記反応式中、Ｒ'－Ｃ＝で示される基は、化合物[III]との反応によって、化合物[Ｉ]のＲ^{6}に変換する。すなわち、Ｒ'は－ＣＨ$_2$－と共にＲ^{6}を形成する基である。化合物[Ｖ]中、Ｘで表されるハロゲンとしては、塩基、臭素が挙げられる。

【００２１】酸による閉環反応は、塩酸、臭化水素酸などのプロトン酸水溶液中、室温～１５０℃で反応させるか、適当な有機溶媒(例、クロロホルム、トルエンなど)中、塩化水素ガスや三フッ化ホウ素エーテラート(ＢＦ$_3$・Ｅｔ$_2$Ｏ)などで、－５℃～１５０℃で反応させることにより行う。ハロゲンによる閉環反応は、臭素などを用い、ハロゲン化炭素(例、クロロホルム、塩化メチレンなど)または酢酸などの有機溶媒中、所望により酢酸ナトリウムあるいはトリエチルアミンなどの塩基の存在下、－５℃～１００℃で反応させることにより行う。過酸による閉環反応はｍ－クロロ過安息香酸などの過酸を用い、塩化メチレンなどの有機溶媒中、所望によりトリエチルアミンなどの塩基の存在下、－１０～５０℃で行う。

【００２２】また、フェノール誘導体とアリルアルコール誘導体のフリーデルクラフト反応は、ジクロロエタンなどの有機溶媒中、硫酸、トリフルオロメタンスルホン酸、三フッ化ホウ素エートラートの存在下、０～１５０℃で行う。

【００２３】ニトロ化合物の還元は、パラジウムカーボンなどの触媒を用いた接触水素添加、酸（例えば塩酸、酢酸など）、または塩基（例えば水酸化ナトリウムなど）の存在下、鉄、亜鉛、すずなどの金属を用いた還元、酢酸などの酸の存在下、三塩化チタンによる還元などにより行うことができ、またジアゾ化合物の還元は、同様の水素添加反応や、ハイドロサルファイトナトリウムなどの還元剤で、水または有機溶媒中、０～１００℃で処理することにより行える。酸化反応は、ジメチルスルホキシドと塩化オキサリルより得られる酸化剤、三酸化クロムなどの酸化剤を用いて、所望によりトリエチルアミンなどの塩基の存在下、塩化メチレン、アセトンなどの有機溶媒中、－７８℃～２５℃で行う。

【００２４】付加－脱離反応(ビッティッヒ反応)を行う場合は、塩基として水素化ナトリウム、水酸化ナトリウム、ナトリウムアルコラート、ｎ－ブチルリチウム、リチウムジイソプロピルアミドなどを用い、ジメチルホルムアミド、テトラヒドロフラン、ジメトキシエタンなどの溶媒中で行い、反応温度は－７８℃～８０℃で、反応時間は約０.５から２４時間である。また、二重結合を水素添加する場合には、パラジウムカーボンなどの触媒を用い、常法に従って目的化合物を得ることができる。

【００２５】水酸基の保護基の脱離(加水分解)は、通常のエステル加水分解条件で行うことができるが、生成物が塩基性条件下で酸素に対して不安定な場合には、アルゴン雰囲気下で反応を行うことにより、良好な収率で目的の加水分解物を得ることができる。アシル化は、所望のアシル化剤(酸無水物、酸ハロゲン化物など)を、要すれば、塩基触媒(好ましくは、水素化ナトリウム、炭酸カリウム、ピリジン、トリエチルアミンなど)あるいは酸触媒(例、硫酸、塩化水素など)の存在下、有機溶媒(例、ジメチルホルムアミド、アセトン、テトラヒドロフラン)中で反応させて行う。反応温度は約－１０から１００℃、反応時間は約１０分から１５時間である。置換基交換反応を行う場合には、例えば、ハロゲンによって閉環した２－ハロメチル－２,３－ジヒドロベンゾフラン誘導体にアミン、チオール、アルコールなどを無溶媒、あるいは、ジメチルホルムアミドやトルエンなどの有機溶媒中で、必要に応じ、塩基（水素化ナトリウムなど）を用い、－５℃～２００℃で反応させることにより行う。反応容器として、必要に応じオートクレーブを用いる。アルキル化反応の例としては、アミノ基や水酸基のアルキル化等が挙げられる。アルキル化には、ハロゲン化アルキル（ハロゲンとしては塩素、臭素、ヨウ素）、硫酸やスルホン酸のアルキルエステル、亜リン酸のアルキルエステル等が用いられる。アルキル化剤は、通常１～２倍量用いられ、反応は、無機塩基（例、水酸化ナトリウム、水酸化カリウム、炭酸カリウム、炭酸ナトリウム等）や有機塩基（例、トリエチルアミン、ピリジン等）の存在下で行なわれる。この時用いる溶媒は、特に限定されないが、テトラヒドロフラン、ジオキサン、ジメチルホルムアミド、ジメチルアセトアミド等の有機溶媒や水が用いられる。反応は、通常室温～１００℃で行なわれる。本発明の原料化合物[II]、[III]、[IV]および[Ｖ]は、特表昭６２－５０２３３３号公報に記載の方法、自体公知の方法、または後記の参考例に示す方法により製造できる。

【００２６】かくして得られる化合物(Ｉ)は、通常の分離・精製手段(例、抽出、クロマトグラフィー、再結晶など)により単離することができる。なお、化合物(Ｉ)がジアステレオマーとして存在する場合は、所望によ

り、前記分離・精製手段によりそれぞれを単離することができる。また、化合物(Ｉ)が光学活性体である場合は、通常の光学分割手段により、d体、l体に分離することができる。

【００２７】本発明の化合物[Ｉ]は、多価不飽和脂肪酸(リノール酸、γ－リノレン酸、α－リノレン酸、アラキドン酸、ジホモ－γ－リノレン酸、エイコサペンタエン酸)の代謝改善、特に、過酸化脂質生成反応を抑制する作用(抗酸化作用)、５－リポキシゲナーゼ系代謝産物[例、ロイコトリエン類、５－ヒドロペルオキシエイコサテトラエン酸(ＨＰＥＴＥ)、５－ヒドロキシエイコサテトラエン酸(ＨＥＴＥ)、リポキシン類、ロイコトキシン類など]の生成抑制作用、トロンボキサンA_2合成酵素の阻害作用、プロスタグランジンI_2合成酵素保持促進作用、LTD_4受容体拮抗作用、活性酸素種の消去作用などの循環系改善作用や抗アレルギー作用を有する。前記のこれらの作用のうち、とりわけ、本発明の化合物[Ｉ]は、過酸化脂質生成反応抑制作用(抗酸化作用)を顕著に示す傾向にある。

【００２８】また、化合物[Ｉ]の毒性、副作用は低い。従って、本発明の化合物[Ｉ]は哺乳動物(マウス、ラット、ウサギ、イヌ、サル、ヒトなど)における血小板凝集による血栓症、心、肺、脳、腎における動脈血管平滑筋の収縮あるいは血管れん縮による虚血性疾患(例えば、心筋梗塞、脳卒中)、神経変性疾患(例、パーキンソン病、アルツハイマー病、ルー・ゲーリッヒ氏病、筋ジストロフィ)、頭部外傷、脊髄外傷など中枢損傷にともなう機能障害、記憶障害や情動障害(酸欠、脳損傷、脳卒中、脳梗塞、脳血栓等により惹起される神経細胞壊死などにともなう障害)、脳卒中、脳梗塞後や脳外科手術、頭部外傷後に起こるけいれんおよびてんかん、腎炎、肺不全、気管支喘息、炎症、動脈硬化、アテローム変性動脈硬化、肝炎、急性肝炎、肝硬変、過敏症肝臓炎、免疫不全症、活性酸素種(スーパーオキサイド、水酸化ラジカルなど)による酵素、生体組織、細胞などの障害によって引き起こされる循環器系疾患(心筋梗塞、脳卒中、脳浮腫、腎炎など)、組織繊維化現象や発癌などの諸疾患に対して治療および予防効果を有し、例えば、抗血栓剤、抗血管れん縮剤、抗喘息剤、抗アレルギー剤、心、脳の循環器系改善剤、腎炎治療剤、肝炎治療剤、組織繊維化阻止剤、活性酸素種消去剤、アラキドン酸カスケード物質調節改善剤などの医薬として有用である。

【００２９】化合物[Ｉ]は、そのままもしくは自体公知の薬学的に許容される担体、賦形剤などと混合した医薬組成物(例、錠剤、カプセル剤、液剤、注射剤、坐剤)として経口的もしくは非経口的に安全に投与することができる。投与量は投与対象、投与ルート、症状などによっても異なるが、例えば、成人の循環器系疾患の患者に対して経口投与するときは、通常１回量として約０．１mg／kg～２０mg／kg体重程度、好ましくは０．２mg／kg～１０mg／kg体重程度を１日１～３回程度投与するのが好都合である。

【００３０】

【実施例】つぎに、実施例、参考例および試験例を挙げて本発明をさらに詳しく説明するが、本発明はこれらに限定されるものではない。

実施例 1

5-アミノ-2-ベンジル-2,4,6,7-テトラメチル-2,3-ジヒドロベンゾフラン

4-アミノ-2,3,5-トリメチルフェノール(20.0g, 0.13mol)、2-メチル-3-フェニル-2-プロペノール(25.0g, 0.17mol)のジクロロメタン(100ml)溶液に硫酸(15ml)を加え、1時間加熱還流した。反応液は飽和炭酸水素ナトリウム水で中和し、生成物を酢酸エチルで抽出した。抽出液は、水洗、乾燥後、溶媒を留去した。残渣をシリカゲルカラムクロマトグラフィー(イソプロピルエーテル)で精製し、ヘキサンから結晶化させて目的物7.2g(収率 19.3%)を得た。融点 68-69℃。

NMR (CDCl$_3$) δ 1.38(3H,s),2.06(3H,s),2.10(3H,s),2.16(3H,s),2.80(2H,broads),2.85(2H,d,J=13.6Hz),3.08(2H,d,J=13.6Hz),7.26(5H,m)。

【００３１】実施例 2

5-アミノ-2,2,4,6,7-ペンタメチル-2,3-ジヒドロベンゾフラン塩酸塩

4-アミノ-2,3,5-トリメチルフェノール(2.0g,13.2mmol)と2-メチル-2-プロペノール(1.15g,15.8mmol)とをジクロロメタン(20ml)中で、硫酸(2ml)とともに18時間加熱還流した。反応液は飽和炭酸水素ナトリウム水で洗浄し、乾燥後濃縮した。残渣をシリカゲルカラムクロマトグラフィー(イソプロピルエーテル)で精製し、塩酸塩にした後エタノール-イソプロピルエーテルから結晶化させて目的物460mg(収率 14.4%)を得た。融点 248-250℃(decomp)。

NMR (DMSO-d$_6$) δ 1.47(6H,s),2.08(3H,s),2.18(6H,s),3.03(2H,s),9.80(2H,broad s)。

【００３２】実施例 3

5-アミノ-2,2,4,6,7-ペンタメチル-2,3-ジヒドロベンゾフラン塩酸塩

4-ホルミルアミノ-2,3,5-トリメチル-1-(2-メチル-2-プロペニルオキシ)ベンゼン(7.33g, 35.7mmol)をメタノール(100ml)に溶解し、氷冷下、これに濃塩酸(30ml)を加えた。フラスコ内をアルゴンで置換した後、2時間加熱還流した。反応液を冷却後重曹水で中和し、クロロホルム抽出した。抽出液を水洗、洗浄後減圧濃縮し、残渣をイソプロピルエーテルから結晶化させ、6.40g(収率 99.2%)を得た。一部を塩酸塩にした後メタノールから再結晶した。融点 248-250℃(分解)。

NMR (DMSO-d$_6$) δ 1.41(6H,s),2.02(3H,s),2.20(6H,s),2.96(2H,s),9.65(2H,broad s)。

【００３３】実施例 4

5-アミノ-2,2,4,6-テトラメチル-7-(2-メチル-1-プロペニル)-2,3-ジヒドロベンゾフラン塩酸塩
上記の方法に従って合成した。収率 80.1%。融点207-208℃(エタノール)。
NMR (DMSO-d6) δ 1.39(6H,s),1.46(3H,s),1.86(3H,s),2.13(3H,s),2.21(3H,s),2.97(2H,s),5.90(1H,s),9.38(2H,broad s)。
【００３４】実施例 5
5-アセチルアミノ-2,2,6,7-テトラメチル-4-ニトロ-2,3-ジヒドロベンゾフラン
参考例 48の方法に従って合成した。収率 89.4%。融点203℃(ジクロロメタン-イソプロピルエーテル)。
NMR (CDCl3) δ 1.48(6H,s),2.15(3H,s),2.18(3H,s),2.19(3H,s),3.29(2H,s),7.79(1H,broad s)。
【００３５】実施例 6
5-アセチルアミノ-2,2,4,7-テトラメチル-6-ニトロ-2,3-ジヒドロベンゾフラン
上記の方法に従って合成した。収率 77.6%。融点 203-204℃(ジクロロメタン-イソプロピルエーテル)。
NMR (CDCl3) δ 1.50(6H,s),2.09(3H,s),2.12(3H,s),2.14(3H,s),3.00(2H,s),7.09(1H,s)。
【００３６】実施例 7
7-アミノ-2,2,4,5,6-ペンタメチル-2,3-ジヒドロベンゾフラン塩酸塩
2,2,4,5,6-ペンタメチル-7-ニトロ-2,3-ジヒドロベンゾフラン(310mg, 1.3mmol)をエタノール(10ml)に溶かし、5% パラジウム炭素(0.6g)を触媒として接触還元反応を行った。触媒をろ去後、ろ液を濃縮し、残渣をシリカゲルカラムクロマトグラフィー（ヘキサン-イソプロピルエーテル、7:3）で精製し、塩酸塩にした後エタノール-イソプロピルエーテルから結晶化させて、目的物170mg(収率 53.5%)を得た。融点 207-212℃。
NMR (DMSO-d6) δ 1.47(6H,s),2.08(3H,s),2.12(3H,s),2.18(3H,s),3.03(2H,s),9.80(2H,broad s)。
【００３７】実施例 8
5-アミノ-2,2,4,6,7-ペンタメチル-3-フェニル-2,3-ジヒドロベンゾフラン
2,2,4,6,7-ペンタメチル-5-ニトロ-3-フェニル-2,3-ジヒドロベンゾフラン(2.0g, 6.4mmol)をエタノール(15ml)に溶かし、5% パラジウム炭素(2.0g)を触媒として接触還元反応を行った。触媒をろ去後、ろ液を濃縮し、残渣をシリカゲルカラムクロマトグラフィー（イソプロピルエーテル）で精製し、続いてヘキサンから結晶化させて目的物1.33g(収率 73.6%)を得た。融点131-132℃。
NMR (CDCl3) δ 1.00(3H,s),1.48(3H,s),1.77(3H,s),2.12(3H,s),2.19(3H,s),3.10(2H,broad s),4.11(1H,s),6.95(2H,m),7.20(3H,m)。
【００３８】実施例 9
5-アミノ-3-(4-フルオロフェニル)-2,2,4,6,7-ペンタメチル-2,3-ジヒドロベンゾフラン
上記の方法に従って合成した。収率 70.2%。融点 126-127℃(ヘキサン)。
NMR (CDCl3) δ 0.99(3H,s),1.47(3H,s),1.77(3H,s),2.12(3H,s),2.18(3H,s),3.10(2H,broad s),4.09(1H,s)6.93(4H,m)。
【００３９】実施例 10
5-アミノ-3-(4-イソプロピルフェニル)-2,2,4,6,7-ペンタメチル-2,3-ジヒドロベンゾフラン
上記の方法に従って合成した。収率 85.0%。融点 134-135℃(ヘキサン)。
NMR (CDCl3) δ 1.00(3H,s),1.22(6H,d,J=6.8Hz),1.47(3H,s),1.78(3H,s),2.13(3H,s),2.19(3H,s),2.85(1H,septet,J=6.8Hz),3.10(2H,broad s),4.08(1H,s),6.85(2H,m),7.07(2H,d,J=8.0Hz)。
【００４０】実施例 11
5-アミノ-2,2,4,6,7-ペンタメチル-3-(3-ピリジル)-2,3-ジヒドロベンゾフラン
上記の方法に従って合成した。収率 53.8%。融点130-131℃(ヘキサン)。
NMR (CDCl3) δ 1.02(3H,s),1.50(3H,s),1.77(3H,s),2.12(3H,s),2.19(3H,s),3.04(2H,broad s),4.12(1H,s),7.16(2H,m),8.36(1H,m)8.46(1H,t,J=3.2Hz)。
【００４１】実施例 12
5-アミノ-3-(3-アミノ-4-ジメチルアミノフェニル)-2,2,4,6,7-ペンタメチル-2,3-ジヒドロベンゾフラン二塩酸塩
上記の方法に従って合成した。収率 42.4%。無晶形。
NMR (DMSO-d6) δ 1.04(3H,s),1.44(3H,s),1.99(3H,s),2.13(3H,s),2.29(3H,s),3.02(6H,s),4.24(1H,s),6.00-7.50(5H,m),9.85(2H,broad s)。
【００４２】実施例 13
5-アミノ-3-イソプロピル-2,2,4,6,7-ペンタメチル-2,3-ジヒドロベンゾフラン塩酸塩
上記の方法に従って合成した。収率 76.6%。融点 225-230℃(エタノール)。
NMR (DMSO-d6) δ 0.70(3H,d,J=6.6Hz),0.96(3H,d,J=6.6Hz),1.21(3H,s),1.57(3H,s),1.62(1H,m),2.09(3H,s),2.53(3H,s),2.57(3H,s),2.76(1H,d,J=2.8Hz),10.07(2H,broad s)。
【００４３】実施例 14
4,5-ジアミノ-2,2,6,7-テトラメチル-2,3-ジヒドロベンゾフラン塩酸塩
上記の方法に従って合成した。収率 96.9%。融点 248-251℃(エタノール)。
NMR (DMSO-d6) δ 1.39(6H,s),1.93(3H,s),2.09(3H,s),2.82(2H,s),3.36(4H,broad s)。
【００４４】実施例 15
5-アセチルアミノ-6-アミノ-2,2,4,7-テトラメチル-2,3-ジヒドロベンゾフラン
上記の方法に従って合成した。収率 98.7%。融点：155-

157℃(イソプロピルエーテル)。
NMR (CDCl3) δ 1.44(6H,s),1.82 and 2.23(3H,s),2.00-2.05(6H,m),2.87(2H,s),3.75(2H,broad s),6.40 and 6.62((1H,broad s)。
【００４５】実施例 16
5-アセチルアミノ-4-アミノ-2,2,6,7-テトラメチル-2,3-ジヒドロベンゾフラン
上記の方法に従って合成した。91.4%。融点 172-173℃(エタノール-エーテル)。
NMR (CDCl3) δ 1.46(6H,s),1.83 and 2.23(3H,s),2.05-2.09(6H,m),2.83(2H,s)。
【００４６】実施例 17
5-アミノ-2,2,4,6,7-ペンタメチル-3-(4-メチルフェニル)-2,3-ジヒドロベンゾフラン
2,2,4,6,7-ペンタメチル-3-(4-メチルフェニル)-5-ニトロ-2,3-ジヒドロベンゾフラン(1.26g, 3.9mmol)をメタノール(30ml)に溶かし、亜鉛末(1.3g)と1N-水酸化ナトリウム(15ml)を加えて3時間加熱還流した。不溶物をろ去し、水を加えて酢酸エチルで抽出した。抽出液は、水洗乾燥後、溶媒を留去した。残渣はシリカゲルカラムクロマトグラフィー(ヘキサン-イソプロピルエーテル、95:5)で精製し、ヘキサンから結晶化させて目的物 710mg(収率 53.7%)を得た。融点 119-120℃。
NMR (CDCl3) δ 1.00(3H,s),1.47(3H,s),1.78(3H,s),2.13(3H,s),2.20(3H,s),2.31(3H,s),3.20(2H,broad s),4.09(1H,s),6.82(2H,m),7.10(2H,m)。
【００４７】実施例 18
5-アミノ-2,2,4,6,7-ペンタメチル-3-(4-プロピルフェニル)-2,3-ジヒドロベンゾフラン
上記の方法に従って合成した。収率 65.6%。融点 68-69℃(メタノール)。
NMR (CDCl3) δ 0.90(3H,t,J=7.2Hz),0.99(3H,s),1.47(3H,s),1.60(2H,sextet,J=7.2Hz),1.77(3H,s),2.12(3H,s),2.19(3H,s),2.54(2H,t,J=7.2Hz),3.10(2H,broad s),4.09(1H,s),6.82(2H,m),7.03(2H,d,J=8.0Hz)。
【００４８】実施例 19
5-アミノ-2,2,4,6,7-ペンタメチル-3-(4-ペンチルフェニル)-2,3-ジヒドロベンゾフラン
上記の方法に従って合成した。収率 55.6%。融点 67-68℃(メタノール)。
NMR (CDCl3) δ 0.87(3H,t,J=6.6Hz),1.00(3H,s),1.31(4H,m),1.47(3H,s),1.58(2H,m),1.78(3H,s),2.12(3H,s),2.19(3H,s),2.55(2H,t,J=7.2Hz),3.20(2H,broads),4.09(1H,s),6.82(2H,m),7.03(2H,d,J=8.0Hz)。
【００４９】実施例 20
5-アミノ-2,4,6,7-テトラメチル-2-ピペリジノメチル-2,3-ジヒドロベンゾフラン
上記の方法に従って合成した。収率 82.1%。融点 60-61℃(イソプロピルエーテル)。
NMR (CDCl3) δ 1.30-1.60(6H,m),1.42(3H,s),2.07(6H,s),2.10(3H,s),2.35-2.65(6H,m),2.80(1H,d,J=15.9Hz),3.10(2H,broad s),3.11(1H,d,J=15.9Hz)。
【００５０】実施例 21
5-アミノ-2,4,6,7-テトラメチル-2-モルフォリノメチル-2,3-ジヒドロベンゾフラン
上記の方法に従って合成した。収率 38.0%。融点 114-115℃(イソプロピルエーテル)。
NMR (CDCl3) δ 1.42(3H,s),2.07(9H,s),2.40-2.70(6H,m),2.81(1H,d,J=15.0Hz),3.13(1H,d,J=15.0Hz),3.20(2H,broad s),3.67(4H,t,J=4.6Hz)。
【００５１】実施例 22
5-アミノ-2,4,6,7-テトラメチル-2-[2-(ジメチルアミノ)エチル]-2,3-ジヒドロベンゾフラン二塩酸塩
上記の方法に従って合成した。収率 46.5%。融点 200-203℃(分解)(エタノール-イソプロピルエーテル)。
NMR (DMSO-d6) δ 1.41(3H,s),2.06(3H,s),2.17(2H,m),2.22(3H,s),2.24(3H,s),2.74(6H,s),2.96(1H,d,J=16.0Hz),3.11(2H,m),3.16(1H,d,J=16.0Hz),9.78(2H,broad s)。
【００５２】実施例 23
5-アミノ-2,4,6,7-テトラメチル-2-(2-ピペリジノエチル)-2,3-ジヒドロベンゾフラン二塩酸塩
上記の方法に従って合成した。収率 41.9%。融点 260-270℃(分解)(エタノール-イソプロピルエーテル)。
NMR (DMSO-d6) δ 1.41(3H,s),1.76(6H,m),2.06(3H,s),2.22(3H,s),2.23(3H,s),2.23(2H,m),2.84(4H,m),2.95(1H,d,J=15.8Hz),3.05(2H,m),3.15(1H,d,J=15.8Hz),9.65(2H,broad s)。
【００５３】実施例 24
5-アミノ-2,2,4,6-テトラメチル-7-(ジメチルアミノ)メチル-2,3-ジヒドロベンゾフランしゅう酸塩
パラホルムアルデヒド(1.61g, 42.8mmol)のエタノール(10ml)懸濁液に、50%ジメチルアミン水溶液(6.46ml,64.2mmol)を滴下し、この混合物を室温で均一になるまで(30分間) 撹拌した。この溶液を、4-アセチルアミノ-3,5-ジメチル-2-(2-メチル-2-プロペニル)フェノール(4.98g, 21.4mmol)のエタノール(30ml)溶液に滴下し、混合物をアルゴン雰囲気下で3.5時間加熱還流した。反応液を冷却後、減圧下濃縮した。残留物をシリカゲルカラムクロマトグラフィー(クロロホルム-メタノール、95:5)で精製し、目的物5.45g(収率 87.7%)を褐色油状物として得た。これをメタノール(60ml)に溶解し、濃塩酸(20ml)を加え、この混合物をアルゴン雰囲気下で1.5時間加熱還流した。反応液を冷却後、過剰の重曹水を加え、クロロホルム抽出した。抽出液を水洗、乾燥後、濃縮した。残渣をシリカゲルカラムクロマトグラフィー(クロロホルム-メタノール、88:12)で精製し、目的物4.86g(収率 90.5%)を褐色油状物として得た。これをエタノール(3ml)に溶解し、5N水酸化ナトリウム(25ml)を加え、混合物をアルゴン雰囲気下、封管中200℃で13時間撹拌した。

反応液を冷却後水を加え、クロロホルム抽出した。抽出液を水洗、乾燥後、濃縮した。残渣をシリカゲルカラムクロマトグラフィー(クロロホルム-メタノール、88:12)で精製し、1.70g(収率 41.5%)を得た。この一部をシュウ酸塩とした後、エタノールから再結晶し、目的物を得た。融点：178-180℃(エタノール)。

NMR (DMSO-d6) δ 1.39(6H,s),2.02(3H,s),2.07(3H,s),2.74(6H,s),2.93(2H,s),4.13(2H,s),4.52(4H,broad s)。

【００５４】実施例 25

5-アミノ-2,2,4,6-テトラメチル-7-ピペリジノメチル-2,3-ジヒドロベンゾフランしゅう酸塩

上記の方法に従って合成した。収率 47.9%-41.0%-55.7%。融点 110-112℃(エタノール)。

NMR (DMSO-d6) δ:1.44(6H,s),1.62-1.80(6H,m),2.01(3H,s),2.03(3H,s),2.99(2H,s),3.11(4H,broad s),4.09(2H,s),4.48(4H,broad s)。

【００５５】実施例 26

5-アミノ-2,2,4,6-テトラメチル-7-モルフォリノメチル-2,3-ジヒドロベンゾフランしゅう酸塩

上記の方法に従って合成した。収率 55.1%-77.3%-55.2%。融点 118-120℃(エタノール)。

NMR (DMSO-d6) δ 1.38(6H,s),2.01(3H,s),2.08(3H,s),2.85(4H,broad s),2.90(2H,s),3.68(4H,broad s),3.83(2H,s),5.03(4H,broad s)。

【００５６】実施例 27

5-アセチルアミノ-2-ヒドロキシメチル-2,4,6,7-テトラメチル-2,3-ジヒドロベンゾフラン

4-アセチルアミノ-2,3,5-トリメチル-6-(2-メチル−2-プロペニル)フェノール(2.0g,8.1mmol)をジクロロメタン(20ml)に溶かし、氷冷下かき混ぜながらm-クロロ過安息香酸(純度70%,2.2g,8.9mmol)を少しづつ加えた。添加終了後、反応液は室温で1時間かき混ぜ、トリエチルアミン(2ml)を加えた。反応液を水洗し、乾燥後濃縮した。残渣をシリカゲルカラムクロマトグラフィー(酢酸エチル)で精製して目的物1.1g(収率 51.7%)を得た。油状。

NMR ($CDCl_3$) δ 1.43(3H,s),1.96(1H,m),2.07(3H,s),2.09(6H,s),2.20(3H,s),2.81(1H,d,J=15.4Hz),3.16(1H,d,J=15.4Hz),3.63(2H,m),6.66(1H,broad s)。

【００５７】実施例 28

5-ホルミルアミノ-2-ヒドロキシメチル-2,4,6,7-テトラメチル-2,3-ジヒドロベンゾフラン

上記の方法に従って合成した。収率 59.9%。融点 149-150℃(酢酸エチル-ヘキサン)。

NMR (DMSO-d6) δ 1.33(3H,s),1.97(3H,s),1.98(3H,s),2.00(3H,s),2.73(1H,d,J=15.4Hz),3.13(1H,d,J=15.4Hz),3.42(2H,d,J=5.8Hz),5.01(1H,t,J=5.8Hz),7.83(0.2H,d,J=11.6Hz),8.21(0.8H,d,J=1.2H),9.05(0.2H,d,J=11.6Hz),9.20(0.8H,broad s)。

【００５８】実施例 29

2-ブロモメチル-5-ホルミルアミノ-2,4,6,7-テトラメチル-2,3-ジヒドロベンゾフラン

4-ホルミルアミノ-2,3,5-トリメチル-6-(2-メチル−2-プロペニル)フェノール(50g, 0.21mol)と酢酸ナトリウム(30.5g, 0.37mol)とを酢酸(500ml)中に入れ、かき混ぜながら臭素(16,5ml, 0.21mol)を滴下した。反応液は30分間かき混ぜた後、氷水中に注ぎ、生成物を酢酸エチルで抽出した。抽出液は飽和炭酸水素ナトリウム水で洗浄し、乾燥後濃縮した。残渣を酢酸エチルに再溶解し、不溶物をろ去した。ろ液は濃縮し、イソプロピルエーテルを加え析出した結晶をろ取し、目的物44.0g(収率 65.7%)を得た。融点 157-158℃。

NMR ($CDCl_3$) δ 1.61(1.5H,s),1.63(1.5H,s),2.09(3H,s),2.11(3H,s),2.13(1.5H,s),2.16(1.5H,s),2.93(1H,d,J=15.8Hz),3.28(0.5H,d,J=15.8Hz),3.29(0.5H,d,J=15.8Hz),3.51(1H,s),3.53(1H,s),6.77(0.5H,broad s),6.85(0.5H,d,J=12.0Hz),7.96(0.5H,d,J=12.0Hz),8.40(0.5H,d,J=1.4Hz)。

【００５９】実施例 30

5-アセチルアミノ-2-ホルミル-2,4,6,7-テトラメチル-2,3-ジヒドロベンゾフラン

塩化オキサリル(0.45ml,4.7mmol)のジクロロメタン(10ml)溶液を-78℃に冷却し、かき混ぜながらジメチルスルホキシド(1ml)を滴下した。同温度で2時間かき混ぜた後、5-アセチルアミノ-2-ヒドロキシメチル-2,4,6,7-テトラメチル-2,3-ジヒドロベンゾフラン(1.1g,4.2mmol)のジクロロメタン(5ml)溶液を滴下し、さらに30分間かき混ぜた。トリエチルアミン(3.5ml)を加え、10分間かき混ぜた後、反応液を1N-塩酸と飽和炭酸水素ナトリウム水で洗浄した。反応液を乾燥後濃縮し、残渣をシリカゲルカラムクロマトグラフィー(酢酸エチル)で精製し、目的物0.47g(収率 43.1%)を得た。油状。

NMR ($CDCl_3$) δ 1.55(3H,s),2.06(3H,s),2.11(3H,s),2.13(3H,s),2.21(3H,s),2.94(1H,d,J=15.8Hz),3.41(1H,d,J=15.8Hz),6.72(1H,broad s)。

【００６０】実施例 31

2-ホルミル-5-ホルミルアミノ-2,4,6,7-テトラメチル-2,3-ジヒドロベンゾフラン

上記の方法に従って合成した。収率 25.5%。油状。

NMR ($CDCl_3$) δ 1.55(1.5H,s),1.57(1.5H,s),2.08(3H,s),2.12(3H,s),2.15(3H,s),2.94(1H,d,J=15.4Hz),3.41(0.5H,d,J=15.4Hz),3.44(0.5H,d,J=15.4Hz),7.00(1H,m),7.95(0.5H,d,J=12.0Hz),8.34(0.5H,d,J=1.8Hz),9.73(0.5H,s),9.74(0.5H,s)。

【００６１】実施例 32

(Z)-5-アセチルアミノ-2,4,6,7-テトラメチル-2-スチリル-2,3-ジヒドロベンゾフラン

ベンジルトリフェニルホスホニウムクロリド(0.7g, 1.8mmol)のテトラヒドロフラン(10ml)懸濁液を-20℃に冷却し、n-ブチルリチウムヘキサン溶液(1.6M, 1.12ml, 1.8

mmol)を滴下した。反応液を30分間かき混ぜた後、5-アセチルアミノ-2-ホルミル-2,4,6,7-テトラメチル-2,3,-ジヒドロベンゾフラン(0.45g, 1.7mmol)のテトラヒドロフラン(5ml)溶液を滴下し、さらに30分間室温でかき混ぜた。反応液に水を加え、生成物を酢酸エチルで抽出し、抽出液を水洗、乾燥後濃縮した。残渣をシリカゲルカラムクロマトグラフィー(イソプロピルエーテル-酢酸エチル、1:1)で精製し、目的物0.44g(収率 76.2%)を得た。油状。

NMR (CDCl$_3$) δ 1.55(3H,s),1.87(3H,s),1.98(3H,s),2.05(3H,s),2.19(3H,s),2.94(1H,d,J=15.4Hz),3.19(1H,d,J=15.4Hz),5.92(1H,d,J=12.8Hz),6.50(1H,d,J=12.8Hz),6.62(1H,broad s),7.25(5H,m)。

【００６２】実施例 33

(Z)-5-アセチルアミノ-2,4,6,7-テトラメチル-2-[2-(4-フルオロフェニル)エテニル]-2,3-ジヒドロベンゾフラン

上記の方法に従って合成した。収率 81.3%(油状)。

NMR (CDCl$_3$) δ 1.55(3H,s),1.84(3H,s),2.00(3H,s),2.05(3H,s),2.19(3H,s),2.95(1H,d,J=14.0Hz),3.19(1H,d,J=14.0Hz),5.88(1H,d,J=12.6Hz),6.45(1H,d,J=12.6Hz),6.69(1H,broad s),7.00(2H,m),7.26(2H,m)。

【００６３】実施例 34

エチル 3-[5-ホルミルアミノ-2,4,6,7-テトラメチル-2,3-ジヒドロベンゾフラン-2-イル]アクリレート

2-ホルミル-5-ホルミルアミノ-2,4,6,7-テトラメチル-2,3,-ジヒドロベンゾフラン(1.0g, 4.1mmol)、トリエチルホスホノアセテート(0.91g, 4.1mmol)、及び水素化ナトリウム(純度60%, 162mg, 4.1mmol)をジメチルホルムアミド中に加え、室温で1時間かき混ぜた。反応液は水で希釈し、生成物を酢酸エチルで抽出した。抽出液は水洗、乾燥後、溶媒を留去した。残渣をシリカゲルカラムクロマトグラフィー(酢酸エチル-イソプロピルエーテル、1:1)で精製し、目的物0.5g(収率39.0%)を得た。油状。

NMR (CDCl$_3$) δ 1.29(3H,t,J=7.2Hz),1.60(3H,s),2.06(1.5H,s),2.11(1.5H,s),2.13(1.5H,s),2.15(1.5H,s),2.17(3H,s),3.05(1H,d,J=15.4Hz),3.15(1H,d,J=15.4Hz),4.19(2H,d,J=7.2Hz),6.02(1H,d,J=15.6Hz),6.92(0.5H,broad s),6.95(0.5H,d,J=12.0Hz),7.02(1H,d,J=15.6Hz),7.95(0.5H,d,J=12.0Hz),8.39(0.5H,d,J=1.6Hz)。

【００６４】実施例 35

5-アセチルアミノ-2,4,6,7-テトラメチル-2-(2-フェニルエチル)-2,3-ジヒドロベンゾフラン

(Z)-5-アセチルアミノ-2,4,6,7-テトラメチル-2-スチリル-2,3-ジヒドロベンゾフラン(1.0g, 3.0mmol)のエタノール溶液に 5% パラジウム炭素(0.3g)を加え、水素雰囲気下で 1 時間かき混ぜた。 触媒をろ去後ろ液を濃縮し、残渣をシリカゲルカラムクロマトグラフィー (イソプロピルエーテル－酢酸エチル、 1:1) で精製し、目的物0.95g (収率 94.4%)を得た。 油状。

NMR (CDCl$_3$) δ 1.48(3H,s),2.02(2H,m),2.05(3H,s),2.09(3H,s),2.14(3H,s),2.22(3H,s),2.72(2H,m)2.89(1H,d,J=15.4Hz),3.05(1H,d,J=15.4Hz),7.10-7.30(5H,m),7.15(1H,broad s)。

【００６５】実施例 36

5-アセチルアミノ-2-[2-(4-フルオロフェニル)エチル]-2,4,6,7-テトラメチル-2,3-ジヒドロベンゾフラン

上記の方法に従って合成した。収率 90.3%。油状。

NMR (CDCl$_3$) δ 1.47(3H,s),1.98(2H,m),2.06(3H,s),2.10(6H,s),2.20(3H,s),2.69(2H,m),2.90(1H,d,J=15.4Hz),3.05(1H,d,J=15.4Hz),6.70(1H,broad s),6.95(2H,m),7.13(2H,m)。

【００６６】実施例 37

5-アミノ-7-(2-メチルプロピル)-2,2,4,6-テトラメチル-2,3-ジヒドロベンゾフラン塩酸塩

5-アミノ-7-(2-メチル-1-プロペニル)-2,2,4,6-テトラメチル-2,3-ジヒドロベンゾフラン(1.50g, 6.11mmol)のエタノール(100ml)溶液に、10%パラジウム炭素(1.0g)を加え、水素雰囲気下で3時間加熱還流した。反応液を冷却した後、ろ過し、ろ液を濃縮した。残渣をイソプロピルエーテルから結晶化させ、1.45g(収率 95.9%)を得た。これをHCl/EtOHで塩酸塩にした後にエタノールから再結晶し、目的物 0.90g(51.9%)を得た。融点：223-225℃(エタノール)。

NMR (DMSO-d$_6$) δ 0.85(6H,d,J=6.6Hz),1.39(6H,s),1.63-1.84(1H,m),2.21(3H,s),2.22(3H,s),2.38(2H,d,J=7.2Hz),2.96(2H,s),9.54(2H,broad s)。

【００６７】実施例 38

5-ホルミルアミノ-2,2,4,6,7-ペンタメチル-2,3-ジヒドロベンゾフラン

5-アミノ-2,2,4,6,7-ペンタメチル-2,3-ジヒドロベンゾフラン(1.00g, 4.87mmol)をギ酸(20ml)に溶かし、48時間加熱還流した。反応液を減圧下濃縮し、残渣に飽和重曹水を加えた後、これをクロロホルム抽出した。抽出液を飽和食塩水で洗浄後、乾燥し、減圧下濃縮した。残渣をシリカゲルカラムクロマトグラフィー(クロロホルム-メタノール、97:3)で精製し、目的物1.06g(収率 93.3%)を得た。一部をジクロロメタン-イソプロピルエーテルから再結晶し、融点 177-179℃の白色プリズム晶を得た。

NMR (CDCl$_3$) δ 1.46(3H,s),1.48(3H,s),2.09-2.16(9H,m),2.94(2H,s),6.68(1H,broad s),7.97(0.5H,d,J=12.0Hz),8.40(0.5H,d,J=1.4Hz)。

【００６８】実施例 39

5-アセチルアミノ-2,2,4,6,7-ペンタメチル-2,3-ジヒドロベンゾフラン

5-アミノ-2,2,4,6,7-ペンタメチル-2,3-ジヒドロベンゾフラン(1.00g, 4.87mmol)およびトリエチルアミン(640mg, 6.33mmol)のテトラヒドロフラン(20ml)溶液に、アセチルクロリド(460mg, 5.84mmol)を氷冷下滴下し、滴下

終了後4時間撹拌した。反応液に水を加え、クロロホルム抽出した。抽出液を飽和重曹水および飽和食塩水で洗浄後、乾燥し、濃縮した。残留物をシリカゲルカラムクロマトグラフィー(クロロホルム-メタノール、97:3)で精製し、目的物920mg(収率 76.4%)を得た。一部をジクロロメタン-イソプロピルエーテルから再結晶した。融点：190℃(ジクロロメタン-イソプロピルエーテル)。
NMR (CDCl3) δ 1.46(6H,s),1.73 and 2.21(3H,s),2.06(3H,s),2.09(3H,s),2.14(3H,s),2.93(2H,s),6.63(1H,broad s).

【００６９】実施例 40
2,2,4,6,7-ペンタメチル-5-プロピオニルアミノ-2,3-ジヒドロベンゾフラン
上記の方法に従って合成した。収率 99.8%。融点：146℃(ジクロロメタン-イソプロピルエーテル)。
NMR (CDCl3) δ 1.06 and 1.31(3H,t,J=7.4Hz),1.46 and 1.50(6H,s),1.92 and 2.44(2H,q,J=7.4Hz),2.04-2.13(9H,m),2.93(2H,s),6.53 and 6.59(1H,broad s)。

【００７０】実施例 41
5-ブチリルアミノ-2,2,4,6,7-ペンタメチル-2,3-ジヒドロベンゾフラン
上記の方法に従って合成した。収率 70.8%。融点 136-138℃(ジクロロメタン-イソプロピルエーテル)。
NMR (CDCl3) δ 0.87 and 1.05(3H,t,J=7.4Hz),1.46 and 1.51(6H,s),1.74-1.92(2H,m),2.05-2.09(9H,m),2.10-2.12(2H,m),2.39(2H,t,J=7.4Hz),2.93(2H,s),6.52-6.62(1H,m),6.53 and 6.60(1H,broad s)。

【００７１】実施例 42
5-ベンゾイルアミノ-2,2,4,6,7-ペンタメチル-2,3-ジヒドロベンゾフラン
上記の方法に従って合成した。収率 84.5%。融点 263-265℃(ジクロロメタン-イソプロピルエーテル)。
NMR (CDCl3) δ 1.48(6H,s),2.12(6H,s),2.16(3H,s),2.96(2H,s),7.45-7.57(3H,m),7.90-7.96(2H,m)。

【００７２】実施例 43
5-イソブチリルアミノ-2,2,4,6,7-ペンタメチル-2,3-ジヒドロベンゾフラン
上記の方法に従って合成した。収率 92.3%。融点 170-172℃(ジクロロメタン-イソプロピルエーテル)。
NMR (CDCl3) δ 1.30(6H,d,J=7.0Hz),1.46(6H,s),2.03(3H,s),2.08(6H,s),2.61(1H,septet,J=7.0Hz),2.92(2H,s),6.57(1H,broad s)。

【００７３】実施例 44
5-エトキシカルボニルアミノ-2,2,4,6,7-ペンタメチル-2,3-ジヒドロベンゾフラン
上記の方法に従って合成した。収率 74.6%。融点 102-104℃(イソプロピルエーテル-ペンタン)。
NMR (CDCl3) δ 1.31(3H,t,J=7.4Hz),1.45 and 1.46(6H,s),2.09(6H,s),2.13(3H,s),2.93(2H,s),4.20(2H,q,J=7.4Hz),5.87(1H,broad s).

【００７４】実施例 45
5-メタンスルホニルアミノ-2,2,4,6,7-ペンタメチル-2,3-ジヒドロベンゾフラン
上記の方法に従って合成した。収率 65.7%。融点 159-160℃(ジクロロメタン-イソプロピルエーテル)。
NMR (CDCl3) δ 1.47(6H,s),2.10(3H,s),2.25(3H,s),2.28(3H,s),2.93(2H,s),3.03(3H,s),5.70(1H,s)。

【００７５】実施例 46
2,2,4,6,7-ペンタメチル-5-(p-トルエンスルホニルアミノ)-2,3-ジヒドロベンゾフラン
5-アミノ-2,2,4,6,7-ペンタメチル-2,3-ジヒドロベンゾフラン(2.00g, 9.74mmol)およびp-トルエンスルホニルクロリド(2.04g, 10.7mmol)をピリジン(30ml)に溶解し、50℃で1時間撹拌した。反応液を減圧下濃縮し、残渣をクロロホルムに溶解した。これを1N塩酸および飽和食塩水で洗浄後、乾燥し、溶媒を減圧下留去した。残渣ををシリカゲルカラムクロマトグラフィー(ヘキサン-酢酸エチル、97:3)で精製し、粗結晶をジクロロメタン-イソプロピルエーテルから再結晶し、目的物2.41g(収率 68.8%)を得た。融点 219-220℃(ジクロロメタン-イソプロピルエーテル)。
NMR (CDCl3) δ 1.46(6H,s),1.80(3H,s),1.93(3H,s),2.01(3H,s),2.43(3H,s),2.87(2H,s),5.81(1H,s),7.24(2H,d,J=8.4Hz),7.60(2H,d,J=8.4Hz).

【００７６】実施例 47
5-エチルアミノ-2-[2-(4-フルオロフェニル)エチル]-2,4,6,7-テトラメチル-2,3-ジヒドロベンゾフラン
5-アセチルアミノ-2,4,6,7-テトラメチル-2-[2-(4-フルオロフェニル)エチル]-2,3-ジヒドロベンゾフラン(1.2g, 3.4mmol)と水素化リチウムアルミニウムをテトラヒドロフラン(20ml)中に加え、3時間加熱還流した。反応液は氷水中に注ぎ、生成物を酢酸エチルで抽出した。抽出液は水洗、乾燥後溶媒を留去し、残渣をシリカゲルカラムクロマトグラフィー(イソプロピルエーテル-酢酸エチル、2:1)で精製し、目的物0.82g(収率 71.2%)を得た。油状。
NMR (CDCl3) δ 1.21(3H,t,J=7.2Hz),1.47(3H,s),1.98(2H,m),2.11(3H,s),2.14(3H,s),2.19(3H,s),2.70(2H,m),2.84(2H,q,J=7.2Hz),2.85(1H,broad s),2.90(1H,d,J=14.0Hz),3.02(1H,d,J=14.0Hz),6.94(2H,m),7.12(2H,m)。

【００７７】実施例 48
5-メチルアミノ-2,2,4,6,7-ペンタメチル-2,3-ジヒドロベンゾフラン塩酸塩
5-アミノ-2,2,4,6,7-ペンタメチル-2,3-ジヒドロフラン(9.00g, 38.6mmol)のテトラヒドロフラン(150ml)溶液に、水素化アルミニウムリチウム(2.93g, 77.2mmol)を氷冷下加え、アルゴン雰囲気下で5時間加熱還流した。反応液を冷却後 水(4.8ml)を加え、ろ過した。ろ液を減圧下濃縮し、残渣をシリカゲルカラムクロマトグラフィ

一(ヘキサン-酢酸エチル、9:1)で精製し、塩酸塩にした後エタノール-エーテルから再結晶し、目的物4.03g(収率 40.8%)を得た。融点 205-208℃(エタノール-エーテル)。
NMR (CDCl3) δ 1.46(6H,s),2.08(3H,s),2.48(6H,s),2.92(2H,s),2.98-3.02(3H,m),10.57(1H,broad s)。
【００７８】実施例 49
5-エチルアミノ-2,2,4,6,7-ペンタメチル-2,3-ジヒドロベンゾフラン塩酸塩
上記の方法に従って合成した。収率 34.0%。油状。
NMR (CDCl3) δ 1.45(6H,s),1.48(3H,t,J=8.4Hz),2.07(3H,s),2.47(3H,s),2.48(3H,s),2.91(2H,s),3.35-3.48(2H,m),10.53(1H,broad s)。
【００７９】実施例 50
2,2,4,6,7-ペンタメチル-5-プロピルアミノ-2,3-ジヒドロベンゾフラン塩酸塩
上記の方法に従って合成した。収率 43.2%。融点 185-187℃(エタノール-エーテル)。
NMR (CDCl3) δ 0.92(3H,t,J=7.4Hz),1.45(6H,s),1.93-2.06(2H,m),2.07(3H,s),2.47(3H,s),2.48(3H,s),2.91(2H,s),3.15-3.29(2H,m),10.54(1H,broad s)。
【００８０】実施例 51
5-ブチルアミノ-2,2,4,6,7-ペンタメチル-2,3-ジヒドロベンゾフラン塩酸塩
上記の方法に従って合成した。収率 39.7%。融点 158-160℃(エタノール-エーテル)。
NMR (CDCl3) δ：0.86(3H,t,J=7.4Hz),1.23-1.38(2H,m),1.45(6H,s),1.91-2.06(2H,m),2:07(3H,s),2.47(3H,s),2.49(3H,s),2.91(2H,s),3.17-3.32(2H,m),10.57(1H,broad s)。
【００８１】実施例 52
5-ベンジルアミノ-2,2,4,6,7-ペンタメチル-2,3-ジヒドロベンゾフラン塩酸塩
上記の方法に従って合成した。収率 32.3%。融点 155-157℃(エタノール-エーテル)。
NMR (CDCl3) δ 1.44(6H,s),2.02(3H,s),2.10(3H,m),2.20(3H,s),2.82(2H,s),4.56(2H,broad s),7.19-7.32(5H,m),10.89(1H,broad s)。
【００８２】実施例 53
2,2,4,6,7-ペンタメチル-5-(2-メチルプロピル)アミノ-2,3-ジヒドロベンゾフラン塩酸塩
上記の方法に従って合成した。収率 67.1%。油状。
NMR (CDCl3) δ 1.10(6H,d,J=6.6Hz),1.45(6H,s),2.05(3H,s),2.44(3H,s),2.48(3H,s),2.54-2.80(1H,m),2.90(2H,s),2.93-3.04(2H,m),10.39(1H,broad s)。
【００８３】実施例 54
5-アセチルアミノ-4-ジメチルアミノ-2,2,6,7-テトラメチル-2,3-ジヒドロベンゾフラン
5-アセチルアミノ-4-アミノ-2,2,6,7-テトラメチル-2,3-ジヒドロベンゾフラン(5.30g, 21.3mmol)のジメチルホルムアミド(100ml)溶液に、炭酸カリウム(4.42g, 32.0mmol))およびヨウ化メチル(3.99ml, 63.9mmol)を加え、室温で3時間撹拌した。反応液に水を加え、これを酢酸エチルで抽出した。抽出液を水洗、乾燥後、溶媒を減圧下留去した。残渣をシリカゲルカラムクロマトグラフィー（クロロホルム-メタノール、97:3）で精製した後、ジクロロメタン-イソプロピルエーテルから再結晶し、目的物5.52g(収率 93.6%)を得た。融点 186℃。NMR (CDCl3) δ 1.44(6H,s),2.09(6H,s),2.21(3H,s),2.67(6H,s),3.09(2H,s),7.17(1H,broads)。
【００８４】実施例 55
5-アセチルアミノ-2,2,4,7-テトラメチル-6-ジメチルアミノ-2,3-ジヒドロベンゾフラン
上記の方法に従って合成した。収率 93.5%。融点 142-143℃(イソプロピルエーテル)。
NMR (CDCl3) δ 1.46(6H,s),2.04(3H,s),2.10(3H,s),2.20(3H,s),2.78(6H,s),2.90(2H,s),7.05(1H,broad s)。
【００８５】実施例 56
5-アミノ-2,4,6,7-テトラメチル-2-ジメチルアミノメチル-2,3-ジヒドロベンゾフラン
2-ブロモメチル-5-ホルミルアミノ-2,4,6,7-テトラメチル-2,3-ジヒドロベンゾフラン(4.0g, 12.8mmol)のメタノール(20ml)溶液に、50%ジメチルアミン水溶液(20ml)を加え、オートクレーブ中160℃で15時間加熱した。反応液は冷却後水で希釈し、生成物を酢酸エチルで抽出した。抽出液は水洗乾燥後、溶媒を留去した。残渣をシリカゲルカラムクロマトグラフィー(クロロホルム-メタノール、95:5)で精製した後、イソプロピルエーテルから再結晶して目的物2.9g(収率 91.2%)を得た。融点 66-67℃。NMR (CDCl3) δ 1.43(3H,s),2.07(6H,s),2.11(3H,s),2.33(6H,s),2.50(2H,s),2.82(1H,d,J=15.4Hz),3.10(2H,broad s),3.12(1H,d,J=15.4Hz)。
【００８６】実施例 57
5-アミノ-2,4,6,7-テトラメチル-2-ピロリジノメチル-2,3-ジヒドロベンゾフラン
2-ブロモメチル-5-ホルミルアミノ-2,4,6,7-テトラメチル-2,3-ジヒドロベンゾフラン(3.0g, 9.6mmol)に、ピロリジン(20ml)を加え、オートクレーブ中160℃で15時間加熱した。反応液は冷却後水で希釈し、生成物を酢酸エチルで抽出した。抽出液は水洗乾燥後、溶媒を留去した。残渣をシリカゲルカラムクロマトグラフィー(クロロホルム-メタノール、9:1)で精製し、ヘキサンから再結晶して目的物2.2g(収率 83.5%)を得た。融点 85-86℃(分解)。
NMR (CDCl3) δ 1.44(3H,s),1.72(4H,m),2.06(6H,s),2.10(3H,s),2.45-2.65(4H,m),2.68(2H,s),2.81(1H,d,J=15.4Hz),3.16(1H,d,J=15.4Hz),3.18(2H,broad s)。
【００８７】実施例 58
5-アミノ-2,4,6,7-テトラメチル-2-(4-メチルピペラジノ)メチル-2,3-ジヒドロベンゾフラン

上記の方法に従って合成した。収率 76.2%。融点76-77℃(イソプロピルエーテル)。NMR (CDCl 3) δ 1.42(3H,s),2.07(6H,s),2.09(3H,s),2.25(3H,s),2.40(4H,m),2.48(1H,d,J=14.2Hz),2.58(1H,d,J=14.2Hz),2.50-2.80(4H,m),2.80(1H,d,J=15.4Hz),3.11(1H,d,J=15.4Hz),3.25(2H,braod s)。

【００８８】実施例 59

5-アミノ-2,4,6,7-テトラメチル-2-[N-(2-ピペリジノエチル)アミノメチル]-2,3-ジヒドロベンゾフラン

上記の方法に従って合成した。収率 89.2%。融点 102-104℃(ジクロロメタン-イソプロピルエーテル)。

NMR(DMSO-d6) δ 1.44(3H,s),1.50-1.62(6H,m),1.73(3H,broad s),2.06(3H,s),2.08(3H,s),2.11(3H,s),2.36-2.48(8H,m),2.75-2.79(3H,m),3.13-3.22(1H,m)。

【００８９】実施例 60

5-アミノ-2,4,6,7-テトラメチル-2-(N-フェニルアミノメチル)-2,3-ジヒドロベンゾフラン塩酸塩

上記の方法に従って合成した。収率 35.5%。融点 162-168℃(エタノール-エーテル)。

NMR (DMSO-d6) δ 1.45(3H,s),2.00(3H,s),2.20(3H,s),2.22(3H,s),2.90(1H,d,J=16.4Hz),3.22(1H,d,J=16.4Hz),3.31(2H,s),6.61(1H,t,J=7.8Hz),6.74(2H,d,J=7.8Hz),7.08(2H,t,J=7.8Hz),9.78(3H,broad s)。

【００９０】実施例 61

5-アミノ-2-(N-ベンジルアミノメチル)-2,4,6,7-テトラメチル-2,3-ジヒドロベンゾフラン二塩酸塩

上記の方法に従って合成した。収率 64.7%。融点 228-232℃(分解)(エタノール-エーテル)。

NMR (DMSO-d6) δ 1.48(3H,s),2.07(3H,s),2.22(3H,s),2.23(3H,s),2.93(1H,d,J=16.2Hz),3.10(2H,s),3.41(1H,d,J=16.2Hz),4.19(2H,s),7.38-7.42(3H,m),7.60-7.65(2H,m),9.70(3H,broad s)。

【００９１】実施例 62

5-アミノ-2,4,6,7-テトラメチル-2-(N-フェネチルアミノメチル)-2,3-ジヒドロベンゾフラン二塩酸塩

上記の方法に従って合成した。収率 63.1%。融点 178-181℃(エタノール)。

NMR (DMSO-d6) δ 1.52(3H,s),2.08(3H,s),2.23(3H,s),2.24(3H,s),2.95-3.50(8H,s),7.22-7.38(5H,m),9.19 and 9.72(3H,broad s)。

【００９２】実施例 63

5-アミノ-2,4,6,7-テトラメチル-2-[N-(4-フェニルブチル)アミノメチル]-2,3-ジヒドロベンゾフラン二塩酸塩

上記の方法に従って合成した。収率 72.6%。融点 201-202℃(エタノール-エーテル)。

NMR (DMSO-d6) δ 1.50(3H,s),1.53-1.74(4H,m),2.07(3H,s),2.24(6H,s),2.59(2H,t,J=7.0Hz),2.91-3.00(3H,m),3.22(2H,s),3.43(1H,d,J=15.8Hz),7.16-7.29(5H,m),9.08 and 9.88(3H,broad s)。

【００９３】実施例 64

5-アミノ-2,4,6,7-テトラメチル-2-[N-(3-ピリジルメチル)アミノメチル]-2,3-ジヒドロベンゾフラン三塩酸塩

上記の方法に従って合成した。収率 54.6%。融点 208-213℃(分解)(エタノール-エーテル)。

NMR (DMSO-d6) δ 1.51(3H,s),2.09(3H,s),2.23(6H,s),2.95(1H,d,J=16.0Hz),3.28(2H,s),3.50(1H,d,J=16.0Hz),4.43(2H,s),7.97(1H,dd,J=5.4Hz,8.0Hz),8.74(1H,d,J=8.0Hz),8.88(1H,d,J=5.4Hz),9.13(1H,s),9.93(3H,broad s)。

【００９４】実施例 65

5-アミノ-2-(1-イミダゾリル)メチル-2,4,6,7-テトラメチル-2,3-ジヒドロベンゾフラン二塩酸塩

2-ブロモメチル-5-ホルミルアミノ-2,4,6,7-テトラメチル-2,3-ジヒドロベンゾフラン(3.12g, 10mmol)のトルエン(30ml)懸濁液に、イミダゾール(10.0g,147mmol)を加え、オートクレーブ中200℃で15時間加熱した。反応液は水洗乾燥後、溶媒を留去した。残渣をメタノール(30ml)に溶かし、6N-水酸化ナトリウム水を加え、1時間加熱還流した。反応液を水で希釈し、生成物を酢酸エチルで抽出した。抽出液は水洗乾燥後、溶媒を留去した。残渣をシリカゲルカラムクロマトグラフィー(クロロホルム-メタノール、95:5)で精製し、塩酸塩とした後エタノール-イソプロピルエーテルから再結晶して目的物1.3g(収率 37.8%)を得た。融点278-283℃(分解)。

NMR (DMSO-d6) δ 1.41(3H,s),2.08(3H,s),2.24(6H,s),3.09(1H,d,J=16.2Hz),3.23(1H,d,J=16.2Hz),4.54(2H,s),7.66(1H,d,J=1.6Hz),7.73(1H,d,J=1.6Hz),9.19(1H,s),10.8(2H,broad s)。

【００９５】実施例 66

5-アミノ-2,4,6,7-テトラメチル-2-(4-フェニルピペラジノ)メチル-2,3-ジヒドロベンゾフラン

上記の方法に従って合成した。収率 18.3%。融点 94-95℃(イソプロピルエーテル)。NMR (CDCl 3) δ 1.45(3H,s),2.08(6H,s),2.12(3H,s),2.55-2.90(8H,m),2.90-3.50(6H,m),6.80-7.00(3H,m),7.25(2H,m)。

【００９６】実施例 67

5-アミノ-2,4,6,7-テトラメチル-2-(4-フェニルピペリジノ)メチル-2,3-ジヒドロベンゾフラン

上記の方法に従って合成した。収率 57.5%。融点 112-113℃(イソプロピルエーテル)。

NMR (CDCl3) δ 1.47(3H,s),1.75(4H,m),2.09(6H,s),2.13(3H,s),2.15-2.50(4H,m),2.54(1H,d,J=14.0Hz),2.63(1H,d,J=14.0Hz),2.84(1H,d,J=15.2Hz),2.99(1H,m),3.15(1H,d,J=15.2Hz),3.19(2H,braod s),7.27(5H,m)。

【００９７】実施例 68

5-アミノ-2,4,6,7-テトラメチル-2-[4-(ジフェニルメチル)ピペラジノメチル]-2,3-ジヒドロベンゾフラン二塩酸塩

上記の方法に従って合成した。収率 17.7%。融点 193-196℃(分解)(エタノール-エーテル)。

NMR (DMSO-d6) δ 1.50(3H,s),1.99(6H,s),2.21(3H,s),3.03-3.51(12H,m),5.20(1H,broad s),7.33-7.45(6H,m),7.68(4H,broad s)。

【００９８】実施例 69

5-アミノ-2-ベンジルオキシメチル-2,4,6,7-テトラメチル-2,3-ジヒドロベンゾフラン塩酸塩

2-ブロモメチル-5-ホルミルアミノ-2,4,6,7-テトラメチル-2,3-ジヒドロベンゾフラン(2.0g, 6.4mmol)にベンジルアルコール(20ml)と水素化ナトリウム(純度60%, 1.0g, 25mmol)を加え、オートクレーブ中180℃で18時間加熱した。反応液は冷却後水で希釈し、生成物を酢酸エチルで抽出した。抽出液は水洗乾燥後、溶媒を留去した。残渣をシリカゲルカラムクロマトグラフィー(イソプロピルエーテル)で精製し、塩酸塩とした後エタノール-イソプロピルエーテルから結晶化させて目的物0.68g(収率 30.5%)を得た。融点 195-200℃。

NMR (DMSO-d6) δ 1.40(3H,s),2.05(3H,s),2.22(6H,s),2.88(1H,d,J=15.8Hz),3.17(1H,d,J=15.8Hz),3.51(2H,s),4.56(2H,s),7.31(5H,m),9.71(2H,braod s)。

【００９９】実施例 70

5-アミノ-2-メトキシ-2,4,6,7-テトラメチル-2,3-ジヒドロベンゾフラン塩酸塩

上記の方法に従って合成した。収率 49.6%。融点 180-182℃(エタノール-イソプロピルエーテル)。

NMR (DMSO-d6) δ 1.37(3H,s),2.04(3H,s),2.22(6H,s),2.85(1H,d,J=16.0Hz),3.14(1H,d,J=16.0Hz),3.31(3H,s),3.43(2H,s),9.77(2H,braod s)。

【０１００】実施例 71

5-アミノ-2,4,6,7-テトラメチル-2-[2-(ジメチルアミノ)エトキシメチル]-2,3-ジヒドロベンゾフラン二塩酸塩

上記の方法に従って合成した。収率 67.8%。無晶。

NMR (DMSO-d6) δ:1.40(3H,s),2.02(3H,s),2.21(3H,s),2.23(3H,s),2.69(2H,broad s),2.81-3.44(12H,m),9.79(2H,broad s)。

【０１０１】実施例 72

5-ホルミルアミノ-2,4,6,7-テトラメチル-2-フェニルチオメチル-2,3-ジヒドロベンゾフラン

2-ブロモメチル-5-ホルミルアミノ-2,4,6,7-テトラメチル-2,3-ジヒドロベンゾフラン(6.0g, 19.2mmol)とチオフェノールのジメチルホルムアミド(50ml)溶液に、水素化ナトリウム(純度60%, 1.0g, 21.1mmol)を加え、アルゴン雰囲気下80℃で1時間かき混ぜた。反応液は冷却後水で希釈し、生成物を酢酸エチルで抽出した。抽出液は水洗乾燥後、溶媒を留去した。残渣をシリカゲルカラムクロマトグラフィー(イソプロピルエーテル-酢酸エチル、1:1)で精製した後イソプロピルエーテル-ヘキサンから再結晶して、目的物5.54g(収率 83.3%)を得た。融点 130-131℃。

NMR (CDCl3) δ 1.55(1.5H,s),1.56(1.5H,s),2.00(3H,s),2.06(1.5H,s),2.09(1.5H,s),2.11(1.5H,s),2.14(1.5H,s),2.91(1H,d,J=15.8Hz),3.23(0.5H,d,J=15.8Hz),3.43(0.5H,d,J=15.8Hz),3.27(2H,s),6.74(0.5H,broad s),6.84(0.5H,d,J=12.0Hz),7.15-7.40(5H,m),7.97(0.5H,d,J=12.0Hz),8.40(0.5H,1.4Hz)。

【０１０２】実施例 73

2-(4-フルオロフェニル)チオメチル-5-ホルミルアミノ-2,4,6,7-テトラメチル-2,3-ジヒドロベンゾフラン

上記の方法に従って合成した。収率 95.6%。油状。

NMR (CDCl3) δ 1.53(1.5H,s),1.55(1.5H,s),2.05(3H,s),2.06(1.5H,s),2.11(3H,s),2.14(1.5H,s),2.91(1H,d,J=15.8Hz),3.21(2H,s),3.22(0.5H,d,J=15.8Hz),3.25(0.5H,d,J=15.8Hz),6.74(0.5H,broad s),6.82(0.5H,d,J=12.2Hz),6.95(2H,t,J=9.0Hz),7.36(2H,dd,J=5.2Hz and 9.0Hz),7.97(0.5H,d,J=12.2Hz),8.40(0.5H,d,J=1.6Hz)。

【０１０３】実施例 74

5-ホルミルアミノ-2-(4-ヒドロキシフェニル)チオメチル-2,4,6,7-テトラメチル-2,3-ジヒドロベンゾフラン

上記の方法に従って合成した。収率 93.1%。油状。

NMR (CDCl3) δ 1.51(1.5H,s),1.53(1.5H,s),1.99(1.5H,s),2.01(1.5H,s),2.03(1.5H,s),2.07(1.5H,s),2.10(1.5H,s),2.14(1.5H,s),2.84(0.5H,d,J=15.4Hz),2.87(0.5H,d,J=15.8Hz),3.10(0.5H,d,J=15.4Hz),3.11(0.5H,d,J=15.8Hz),3.20(0.5H,d,J=15.8Hz),3.21(0.5H,d,J=15.8Hz),3.22(0.5H,d,J=15.4Hz),3.23(0.5H,d,J=15.8Hz),6.01(0.5H,broad s),6.15(0.5H,broad s),6.70(2H,m),6.81(0.5H,broads),6.85(0.5H,broad s),7.25(2H,m),7.95(0.5H,d,J=11.8Hz),8.39(0.5H,d,J=1.6Hz)。

【０１０４】実施例 75

5-ホルミルアミノ-2,4,6,7-テトラメチル-2-(1-メチル-2-イミダゾリル)チオメチル-2,3-ジヒドロベンゾフラン

上記の方法に従って合成した。収率 88.6%。油状。

NMR (CDCl3) δ 1.53(1.5H,s),1.55(1.5H,s),1.97(1.5H,s),2.03(1.5H,s),2.04(1.5H,s),2.10(3H,s),2.14(1.5H,s),2.89(1H,d,J=15.6Hz),3.18(0.5H,d,J=15.6Hz),3.24(0.5H,d,J=15.6Hz),3.47(2H,s),3.49(1.5H,s),3.52(1.5H,s),6.87(1H,m),6.99(0.5H,d,J=12.0Hz),7.00(1H,m),7.11(0.5H,broad s),7.95(0.5H,d,J=12.0Hz),8.37(0.5H,d,J=1.4Hz)。

【０１０５】実施例 76

2-(2-ベンゾチアゾリル)チオメチル-5-ホルミルアミノ-2,4,6,7-テトラメチル-2,3-ジヒドロベンゾフラン

上記の方法に従って合成した。収率 88.2%。融点 190-192℃(イソプロピルエーテル)。

NMR (CDCl3) δ 1.64(3H,s),2.00(3H,s),2.07(1.5H,s),2.10(1.5H,s),2.11(1.5H,s),2.14(1.5H,s),2.99(1H,d,J=15.8Hz),3.27(0.5H,d,J=15.8Hz),3.29(0.5H,d,J=15.8Hz),3.78(0.5H,d,J=15.4Hz),3.79(0.5H,d,J=15.4Hz),3.87(0.5H,d,J=15.4Hz),3.88(0.5H,d,J=15.4Hz),6.73(0.5

H,broad s),6.75(0.5H,d,J=12.0Hz),7.20-7.50(2H,m),7.70-7.85(2H,m),7.97(0.5H,d,J=12.0Hz),8.40(0.5H,d,J=1.6Hz)。

【０１０６】実施例 77

5-ホルミルアミノ-2,4,6,7-テトラメチル-2-(4-ピリジル)チオメチル-2,3-ジヒドロベンゾフラン

上記の方法に従って合成した。収率 71.6%。油状。

NMR (CDCl3) δ 1.59(1.5H,s),1.61(1.5H,s),1.97(3H,s),2.08(1.5H,s),2.10(1.5H,s),2.13(1.5H,s),2.14(1.5H,s),2.98(1H,d,J=16.0Hz),3.25(0.5H,d,J=16.0Hz),3.30(0.5H,d,J=16.0Hz),3.31(2H,s),7.00(0.5H,d,J=12.0Hz),7.05(0.5H,broads),7.17(2H,dd,J=1.6Hz and 6.2Hz),7.98(0.5H,d,J=12.0Hz),8.36(2H,dd,J=1.6Hz and 6.2Hz),8.37(0.5H,d,J=1.6Hz)。

【０１０７】実施例 78

2-ベンジルチオメチル-5-ホルミルアミノ-2,4,6,7-テトラメチル-2,3-ジヒドロベンゾフラン

上記の方法に従って合成した。収率 83.5%。油状。

NMR (CDCl3) δ 1.49(1.5H,s),1.50(1.5H,s),2.08(1.5H,s),2.12(6H,s),2.16(1.5H,s),2.71(1H,d,J=13.4Hz),2.77(1H,d,J=13.4Hz),2.86(1H,d,J=15.0Hz),3.18(1H,d,J=15.0Hz),3.74(1H,d,J=13.2Hz),3.18(1H,d,J=13.2Hz),6.76(0.5H,broads),6.87(0.5H,d,J=12.0Hz),7.30(5H,m),7.98(0.5H,d,J=12.0Hz),8.40(0.5H,d,J=1.4Hz)。

【０１０８】実施例 79

5-ホルミルアミノ-2,4,6,7-テトラメチル-2-プロピルチオメチル-2,3-ジヒドロベンゾフラン

上記の方法に従って合成した。収率 93.0%。油状。

NMR (CDCl3) δ 0.96(3H,t,J=7.4Hz),1.52(1.5H,s),1.54(1.5H,s),1.60(2H,m),2.08(3H,s),2.10(1.5H,s),2.12(1.5H,s),2.13(1.5H,s),2.16(1.5H,s),2.58(2H,dt,J=7.2 and 1.2Hz),2.82(1H,s),2.84(1H,s),2.89(1H,d,J=15.8Hz),3.22(0.5H,d,J=15.8Hz),3.24(0.5H,d,J=15.8Hz),6.77(0.5H,broad s),6.85(0.5H,d,J=12.0Hz),7.97(0.5H,d,J=12.0Hz),8.40(0.5H,d,J=1.6Hz)。

【０１０９】実施例 80

5-ホルミルアミノ-2-(2-ヒドロキシエチル)チオメチル-2,4,6,7-テトラメチル-2,3-ジヒドロベンゾフラン

上記の方法に従って合成した。収率 57.2%。油状。

NMR (CDCl3) δ 1.52(1.5H,s),1.54(1.5H,s),2.09(3H,s),2.11(1.5H,s),2.12(1.5H,s),2.13(1.5H,s),2.16(1.5H,s),2.29(0.5H,t,J=6.4Hz),2.35(0.5H,t,J=6.4Hz),2.80(2H,dt,J=7.2 and 1.2Hz),2.87(0.5H,s),2.89(1H,s),2.91(1H,d,J=15.4Hz),3.20(0.5H,d,J=15.4Hz),3.22(0.5H,d,J=15.4Hz),3.73(2H,m),6.78(0.5H,broads),6.80(0.5H,d,J=12.0Hz),7.97(0.5H,d,J=12.0Hz),8.38(0.5H,d,J=1.4Hz).

【０１１０】実施例 81

3-[(5-ホルミルアミノ-2,4,6,7-テトラメチル-2,3-ジヒドロベンゾフラン-2-イル)メチルチオ]プロピオン酸

上記の方法に従って合成した。収率 94.7%。油状。

NMR (CDCl3) δ 1.52(1.5H,s),1.54(1.5H,s),2.08(3H,s),2.09(3H,s),2.12(1.5H,s),2.14(1.5H,s),2.64(2H,t,J=7.0Hz),2.86(2H,t,J=7.0Hz),2.87(2H,s),2.90(1H,d,J=15.4Hz),3.22(1H,d,J=15.4Hz),6.50(0.5H,broad s),6.95(0.5H,broad s),7.96(0.5H,broad s),8.38(0.5H,d,J=1.6Hz).

【０１１１】実施例 82

5-ホルミルアミノ-2,4,6,7-テトラメチル-2,3-ジヒドロベンゾフラン-2-イルフェニルスルホキシド

5-ホルミルアミノ-2,4,6,7-テトラメチル-2-フェニルチオメチル-2,3-ジヒドロベンゾフラン(2.3g, 6.7mmol)をメタノール(20ml)に溶かし、1M-メタ過ヨウ素酸ナトリウム水溶液(20ml)を加えて3時間かき混ぜた。反応液は水で希釈し精製物は酢酸エチルで抽出した。抽出液は水洗乾燥後、溶媒を留去した。残渣をイソプロピルエーテル-酢酸エチルから結晶化させて目的物1.54g(収率 64.0%)を得た

。融点 112-115℃。

NMR (CDCl3) δ 1.62(3H,s),2.08(3H,s),2.12(1.5H,s),2.14(1.5H,s),2.16(1.5H,s),2.18(1.5H,s),3.00-3.40(4H,m),6.78(1H,m),7.45-7.70(5H,m),7.96(0.25H,d,J=12.0Hz),7.99(0.25H,d,J=12.0Hz),8.40(0.25H,d,J=1.4Hz),8.42(0.25H,d,J=1.4Hz)。

【０１１２】実施例 83

5-ホルミルアミノ-2,4,6,7-テトラメチル-2,3-ジヒドロベンゾフラン-2-イルフェニルスルホン

5-ホルミルアミノ-2,4,6,7-テトラメチル-2-フェニルチオメチル-2,3-ジヒドロベンゾフラン(2.1g, 6.2mmol)をメタノール(20ml)に溶かし、2M-メタ過ヨウ素酸ナトリウム水溶液(20ml)を加えて3時間加熱還流した。反応液は水で希釈し精製物は酢酸エチルで抽出した。抽出液は水洗乾燥後、溶媒を留去した。残渣をイソプロピルエーテル-酢酸エチルから結晶化させて目的物1.40g(収率 65.9%)を得た。融点 154-155℃。

NMR (CDCl3) δ 1.70(1.5H,s),1.71(1.5H,s),1.81(1.5H,s),1.84(1.5H,s),2.05(1.5H,s),2.07(1.5H,s),2.12(1.5H,s),2.14(1.5H,s),3.01(1H,d,J=15.6Hz),3.56(1H,s),3.58(1H,s),3.62(0.5H,d,J=15.6Hz),3.67(0.5H,d,J=15.6Hz),6.71(0.5H,broad s),6.74(0.5H,d,J=12.0Hz),7.15-7.70(3H,m),7.89(2H,m),7.96(0.5H,d,J=12.0Hz),8.40(0.5H,d,J=1.6Hz)。

【０１１３】実施例 84

5-アミノ-2,4,6,7-テトラメチル-2-(2-フェニルエチル)-2,3-ジヒドロベンゾフラン

5-アセチルアミノ-2,4,6,7-テトラメチル-2-(2-フェニルエチル)-2,3-ジヒドロベンゾフラン(0.7g, 2.1mmol)のメタノール(3ml)溶液に6N-水酸化ナトリウム水溶液(3ml)を加え、オートクレーブ中で18時間200℃に加熱した。反応液を水で希釈し、生成物を酢酸エチルで抽出し

た。抽出液を水洗、乾燥後濃縮し、残渣をシリカゲルカラムクロマトグラフィー(イソプロピルエーテル-酢酸エチル、2:1)で精製した。得られた粗結晶をヘキサンから再結晶して目的物0.32g(収率 54.5%)を得た。融点 45-46℃。

NMR ($CDCl_3$) δ 1.47(3H,s),2.03(2H,m),2.07(3H,s),2.09(3H,s),2.14(3H,s),2.76(2H,m),2.92(1H,d,J=15.4Hz),3.00(2H,broad s),3.07(1H,d,J=15.4Hz),7.10-7.30(5H,m)。

【０１１４】実施例 85

5-アミノ-2,4,6,7-テトラメチル-2-[2-(4-フルオロフェニル)エチル]-2,3-ジヒドロベンゾフラン

上記の方法に従って合成した。収率 54.6%。融点 62-63℃(ヘキサン)。

NMR ($CDCl_3$) δ 1.47(3H,s),1.98(2H,m),2.10(3H,s),2.14(3H,s),2.19(3H,s),2.72(2H,m),2.90(1H,d,J=14.0Hz),3.00(2H,broad s),3.05(1H,d,J=14.0Hz),6.95(2H,m),7.13(2H,m)。

【０１１５】実施例 86

メチル 3-[5-アミノ-2,4,6,7-テトラメチル-2,3-ジヒドロベンゾフラン-2-イル]アクリレート塩酸塩

3-[5-アセチルアミノ-2,4,6,7-テトラメチル-2.3-ジヒドロベンゾフラン-2-イル]アクリル酸エチルエステル(0.5g, 1.58mmol)をメタノール(5ml)に溶かし、濃塩酸(5ml)を加えて1時間加熱還流した。反応液を冷却して析出した結晶をろ過し、得られた粗結晶をエタノール-イソプロピルエーテルから再結晶して目的物0.35g(収率 74.7%)を得た。融点 225-234℃(分解)。

NMR (DMSO-d_6) δ 1.58(3H,s),2.11(3H,s),2.19(3H,s),2.21(3H,s),3.12(1H,d,J=15.0Hz),3.24(1H,d,J=15.0Hz),3.65(3H,s),5.93(1H,d,J=16.0Hz),7.04(1H,d,J=16.0Hz),9.50(2H,broad s)。

【０１１６】実施例 87

5-アミノ-2-ブロモメチル-2,4,6,7-テトラメチル-2,3-ジヒドロベンゾフラン塩酸塩

上記の方法に従って合成した。収率 90.2%。融点 235-245℃(分解)(エタノール-イソプロピルエーテル)。

NMR (DMSO-d_6) δ 1.53(3H,s),2.04(3H,s),2.23(3H,s),2.24(3H,s),3.03(1H,d,J=16.0Hz),3.27(1H,d,J=16.0Hz),3.77(2H,s),9.85(2H,broad s)。

【０１１７】実施例 88

5-アミノ-2-フェニルチオメチル-2,4,6,7-テトラメチル-2,3-ジヒドロベンゾフラン塩酸塩

上記の方法に従って合成した。収率 94.5%。融点 130-131℃(エタノール-イソプロピルエーテル)。

NMR (DMSO-d_6) δ 1.51(3H,s),1.87(3H,s),2.19(3H,s),2.20(3H,s),2.99(1H,d,J=15.8Hz),3.22(1H,d,J=15.8Hz),3.38(2H,s),7.10-7.40(5H,m),9.69(2H,broads)。

【０１１８】実施例 89

5-アミノ-2-(4-フルオロフェニル)チオメチル-2,4,6,7-テトラメチル-2,3-ジヒドロベンゾフラン塩酸塩

上記の方法に従って合成した。収率 80.9%。融点 204-210℃(分解)(エタノール-イソプロピルエーテル)。

NMR (DMSO-d_6) δ 1.49(3H,s),1.84(3H,s),2.19(3H,s),2.20(3H,s),2.98(1H,d,J=15.8Hz),3.21(1H,d,J=15.8Hz),3.31(1H,d,J=14.0Hz),3.39(1H,d,J=14.0Hz);7.13(2H,t,J=9.0Hz),7.38(2H,dd,J=9.0 and 5.4Hz),9.67(2H,broad s)。

【０１１９】実施例 90

5-アミノ-2-(4-ヒドロキシフェニル)チオメチル-2,4,6,7-テトラメチル-2,3-ジヒドロベンゾフラン塩酸塩

上記の方法に従って合成した。収率 96.2%。融点 230-236℃(分解)(エタノール-イソプロピルエーテル)。

NMR (DMSO-d_6) δ 1.46(3H,s),1.91(3H,s),2.18(6H,s),2.94(1H,d,J=15.8Hz),3.20(1H,d,J=15.8Hz),3.20(2H,s),6.70(2H,d,J=8.6Hz),7.19(2H,d,J=8.6Hz),9.45(2H,broad s),9.56(1H,s)。

【０１２０】実施例 91

5-アミノ-2-(1-メチルイミダゾール-2-イル)チオメチル-2,4,6,7-テトラメチル-2,3-ジヒドロベンゾフラン二塩酸塩

上記の方法に従って合成した。収率 65.3%。融点 220-225℃(分解)(エタノール-イソプロピルエーテル)。

NMR (DMSO-d_6) δ 1.50(3H,s),1.72(3H,s),2.19(3H,s),2.24(3H,s),3.05(1H,d,J=16.2Hz),3.29(1H,d,J=16.2Hz),3.50(3H,s),3.56(1H,d,J=14.6Hz),3.84(1H,d,J=14.6Hz),7.71(1H,d,J=1.8Hz),7.75(1H,d,J=1.8Hz),10.2(2H,broad s)。

【０１２１】実施例 92

5-アミノ-2-(2-ベンゾチアゾリル)チオメチル-2,4,6,7-テトラメチル-2,3-ジヒドロベンゾフラン塩酸塩

上記の方法に従って合成した。収率 89.1%。融点 204-208℃(分解)(エタノール-イソプロピルエーテル)。

NMR (DMSO-d_6) δ 1.58(3H,s),1.76(3H,s),2.16(3H,s),2.21(3H,s),3.08(1H,d,J=15.8Hz),3.28(1H,d,J=15.8Hz),3.79(1H,d,J=14.6Hz),3.88(1H,d,J=14.6Hz),7.37(1H,t,J=7.6Hz),7.47(1H,t,J=7.6Hz),7.78(1H,d,J=7.6Hz),8.01(1H,d,J=7.6Hz),9.65(2H,broad s)。

【０１２２】実施例 93

5-アミノ-2-ベンジルチオメチル-2,4,6,7-テトラメチル-2,3-ジヒドロベンゾフラン塩酸塩

上記の方法に従って合成した。収率 74.1%。融点 170-172℃(エタノール-イソプロピルエーテル)。

NMR (DMSO-d_6) δ 1.44(3H,s),2.07(3H,s),2.23(6H,s),2.80(2H,s),2.93(1H,d,J=16.0Hz),3.13(1H,d,J=16.0Hz),3.77(1H,d,J=13.8Hz),3.87(1H,d,J=13.8Hz),7.29(5H,m),9.77(2H,broad s)。

【０１２３】実施例 94

5-アミノ-2,4,6,7-テトラメチル-2-(4-ピリジル)チオメチル-2,3-ジヒドロベンゾフラン

上記の方法に従って合成した。収率 80.4%。融点 96-97℃(酢酸エチル-イソプロピルエーテル)。
NMR (CDCl3) δ 1.58(3H,s),2.00(3H,s),2.05(3H,s),2.06(3H,s),2.85(2H,broads),2.98(1H,d,J=15.6Hz),3.21(1H,d,J=15.6Hz),3.25(1H,d,J=14.0Hz),3.32(1H,d,J=14.0Hz),7.14(2H,dd,J=4.8 and 2.0Hz),8.33(2H,dd,J=4.8 and 2.0Hz)。

【０１２４】実施例 95
5-アミノ-2,4,6,7-テトラメチル-2-プロピルチオメチル-2,3-ジヒドロベンゾフラン塩酸塩
上記の方法に従って合成した。収率 74.6%。融点 186-188℃(エタノール-イソプロピルエーテル)。
NMR (DMSO-d6) δ 0.97(3H,t,J=7.4Hz),1.40-1.70(2H,m),1.53(3H,s),2.09(3H,s),2.50(6H,s),2.45-2.60(2H,m),2.82(2H,s),2.88(1H,d,J=15.4Hz),3.28(1H,d,J=15.4Hz),10.10(2H,broad s)。

【０１２５】実施例 96
5-アミノ-2-(2-ヒドロキシエチル)チオメチル-2,4,6,7-テトラメチル-2,3-ジヒドロベンゾフラン
上記の方法に従って合成した。収率 32.3%。融点 108-109℃(酢酸エチル-イソプロピルエーテル)。
NMR (CDCl3) δ 1.51(3H,s),2.07(3H,s),2.08(3H,s),2.11(3H,s),2.80(1H,broads),2.81(2H,t,J=5.4Hz),2.82(1H,d,J=15.0Hz),2.90(1H,d,J=15.0Hz),2.92(1H,d,J=15.4Hz),3.19(1H,d,J=15.4Hz),3.20(2H,broad s),3.73(2H,t,J=5.4Hz)。

【０１２６】実施例 97
3-[(5-アミノ-2,4,6,7-テトラメチル-2,3-ジヒドロベンゾフラン-2-イル)メチルチオ]プロピオン酸
上記の方法に従って合成した。収率 77.5%。融点 139-140℃(酢酸エチル-イソプロピルエーテル)。
NMR (CDCl3) δ 1.51(3H,s),2.07(6H,s),2.09(3H,s),2.64(2H,t,J=6.8Hz),2.80(1H,d,J=14.0Hz),2.87(1H,d,J=14.0Hz),2.88(2H,t,J=6.8Hz),2.91(1H,d,J=15.4Hz),3.20(1H,d,J=15.4Hz),4.90(3H,broad s)。

【０１２７】実施例 98
5-アミノ-2,4,6,7-テトラメチル-2,3-ジヒドロベンゾフラン-2-イル フェニルスルホキシド
上記の方法に従って合成した。収率 21.0%。油状。
NMR (CDCl3) δ 1.60(1.5H,s),1.84(1.5H,s),2.04(1.5H,s),2.09(4.5H,s),2.11(3H,s),2.90-3.45(5.5H,m),3.69(0.5H,d,J=15.8Hz),7.48(3H,m),7.63(2H,m)。

【０１２８】実施例 99
5-アミノ-2,4,6,7-テトラメチル-2,3-ジヒドロベンゾフラン-2-イル フェニルスルホン
上記の方法に従って合成した。収率 91.7%。融点 150-151℃(酢酸エチル-イソプロピルエーテル)。
NMR (CDCl3) δ 1.69(3H,s),1.81(3H,s),2.02(3H,s),2.05(3H,s),2.99(1H,d,J=15.6Hz),3.30(2H,broad s),3.54(2H,s),3.60(1H,d,J=15.6Hz),7.40-7.70(3H,m),7.85(2H,m)。

【０１２９】実施例 100
5-アミノ-2,2,6,7-テトラメチル-4-ニトロ-2,3-ジヒドロベンゾフラン塩酸塩上記の方法に従って合成した。収率 79.6%。融点 119-121℃(エタノール-エーテル)。
NMR (CDCl3) δ 1.48(6H,s),2.20(3H,s),2.54(3H,s),3.42(2H,s),8.61(2H,broads)。

【０１３０】実施例 101
5-アミノ-2,2,6,7-テトラメチル-4-ジメチルアミノ-2,3-ジヒドロベンゾフラン二塩酸塩
上記の方法に従って合成した。収率 64.5%。融点 240-244℃(エタノール)。
NMR(DMSO-d6) δ 1.42(6H,s),2.02(3H,s),2.18(3H,s),2.63(6H,s),3.17(2H,s),4.94(2H,broad s)。

【０１３１】実施例 102
5-アミノ-2,2,4,7-テトラメチル-6-ジメチルアミノ-2,3-ジヒドロベンゾフラン塩酸塩
上記の方法に従って合成した。収率 63.2%。融点 236-238℃(エタノール)。
NMR (DMSO-d6) δ：1.41(6H,s),2.10(3H,s),2.19(3H,s),2.72(6H,s),2.96(2H,s),9.66(2H,broad s)。

【０１３２】実施例 103
5-アミノ-2,2,4,6,7-ペンタメチル-2,3-ジヒドロベンゾフラン
4-アミノ-2,3,5-トリメチルフェノール２.０g(１３.２ミリモル)、２－メチル－２－プロペノール１.１５g(１５.８ミリモル)のジクロロメタン(２０ml)溶液に、硫酸２.０mlを加え、アルゴン雰囲気下１８時間加熱還流した。反応液を飽和炭酸水素ナトリウム水で弱アルカリ性とし、有機層を分けた。有機層を水洗、乾燥後、濃縮し、残渣をシリカゲルカラムクロマトグラフィー(イソプロピルエーテルで溶出)で精製し、得られた生成物をヘキサンから再結晶して、5-アミノ-2,2,4,6,7-ペンタメチルクマランの結晶４６０mg(収率１６.９%)を得た。融点１１０～１１１℃。
NMR(CDCl3) δ：１．４５（６H，ｓ），２．０６（３H，ｓ），２．０９（３H，ｓ），２．１３（３H，ｓ），２．９４（２H，ｓ），３．２６（２H，ｂｒｏａｄ ｓ）。

【０１３３】実施例 １０４
2，2，4，6，７－ペンタメチル-5-フェニルアミノ-2,3-ジヒドロベンゾフラン
3,5,6-トリメチル-2-(2-メチル-2-プロペニル)-4-フェニルアミノフェノール(1.40g、4.98mmol)のメタノール(30ml)溶液に、氷冷下、濃塩酸(10ml)を加え、混合物をアルゴン雰囲気下で30分間加熱還流した。反応液を冷却した後重曹水で中和し、酢酸エチルで抽出した。抽出液を飽和食塩水で洗浄した後乾燥、濃縮した。残渣をイソプロピルエーテルから再結晶し、目的物0.97g(収率 69.3%)を得た。融点 148-151℃。

NMR (CDCl3) δ 1.49(6H,s),2.04(3H,s),2.10(3H,s),2.12(3H,s),2.95(2H,s),5.03(1H,broad s),6.42-6.48(2H,m),6.64-6.72(1H,m),7.08-7.17(2H,m)。

【0134】実施例 105

5-(4-クロロフェニルアミノ)-2,2,4,6,7-ペンタメチル-2,3-ジヒドロベンゾフラン

実施例104と同様の方法に従って合成した。収率 60.0%。融点 106-107℃(イソプロピルエーテル-ペンタン)。

NMR (CDCl3) δ 1.49(6H,s),2.02(3H,s),2.07(3H,s),2.12(3H,s),2.95(2H,s),5.04(1H,broad s),6.36(2H,d,J=8.8Hz),7.06(2H,d,J=8.8Hz)。

【0135】実施例 106

5-(4-メトキシフェニルアミノ)-2,2,4,6,7-ペンタメチル-2,3-ジヒドロベンゾフラン

実施例104と同様の方法に従って合成した。収率 61.2%。融点 117-119℃(イソプロピルエーテル-ペンタン)。

NMR (CDCl3) δ 1.49(6H,s),2.04(3H,s),2.09(3H,s),2.12(3H,s),2.95(2H,s),3.73(3H,s),4.86(1H,broad s),6.41(2H,d,J=9.0Hz),6.73(2H,d,J=9.0Hz)。

【0136】参考例 1

4-アミノ-2,3,5-トリメチルフェノール

スルファニル酸 (49.4g, 258mmol)の水(250ml)溶液に、室温でかき混ぜながら固体 Na_2CO_3 (13.7g, 129mmol) を少しづつ加え、反応液が均一な溶液になった後(溶けない場合は少し加温してもよい)、氷冷し$NaNO_2$ (19.4g, 280mmol)の水(50ml)溶液を加えた(内温10℃以下)。次にこの溶液を滴下ロートに入れ、氷冷下かき混ぜながら濃塩酸(46ml)と氷(100g)の上に約10分間で滴下した(滴下ロートの内温は10℃以下)。滴下終了後、氷冷を続けながら反応液を30分間かき混ぜた。次に機械式撹拌機を備えた別の反応容器に水(250ml)、NaOH(56.8g, 142mmol)及び2,3,5-トリメチルフェノール(35.3g, 259mmol)を入れ、窒素気流下かき混ぜながら-10℃から5℃の範囲で先の反応液を滴下した(滴下ロートの内容物の温度が10℃を越えないように適宜氷を加えて冷却。約15分間で滴下)。滴下終了後、反応液を50℃に加温し、$Na_2S_2O_4$ (11.9g, 68.3mmol)を加えた。続いて反応液を80℃に加温し、更に$Na_2S_2O_4$ (214.2g, 1.23mol)を5等分して5分間隔で加えた。反応液は30分間、同温度でかき混ぜた後冷却し、析出した結晶をろ取した。得られた結晶を水洗し、乾燥後酢酸エチル-イソプロピルエーテルから再結晶して目的物33.0g(収率 84.2%)を得た。融点 153-154℃。

NMR (CDCl3) δ 2.11(6H,s),2.16(3H,s),3.55(3H,broad s),6.42(2H,s)。

【0137】参考例 2

4-アミノ-2,5-ジメチルフェノール

上記の方法に従って合成した。収率 59.7%。融点 216-220℃(水)。

NMR (DMSO-d6) δ 1.94(3H,s),1.97(3H,s),4.06(2H,broad s),6.33(1H,s),6.38(1H,s),8.04(1H,s)。

【0138】参考例 3

4-アミノ-3,5-ジメチルフェノール

上記の方法に従って合成した。収率 52.2%。融点 190-191℃(水)。

NMR (DMSO-d6) δ 2.01(6H,s),3.90(2H,broad s),6.28(2H,s),8.19(1H,s)。

【0139】参考例 4

4-ホルミルアミノ-2,3,5-トリメチルフェノール

4-アミノ-2,3,5-トリメチルフェノール(100g, 662mmol)をギ酸(500ml)に溶かし、36時間加熱還流した。反応液を氷水中に注ぎ、析出した結晶をろ取し、水洗、乾燥した。得られた粗結晶はエタノールから再結晶し、目的物85.9g(収率 72.5%)を得た。融点 219-220℃。

NMR (CDCl3) δ 2.00(3H,s),2.03(6H,s),6.53(1H,s),8.20(1H,d,J=1.8Hz),9.06(1H,s),9.15(1H,broad s)。

【0140】参考例 5

4-ホルミルアミノ-3,5-ジメチルフェノール

上記の方法に従って合成した。収率 70.3%。融点 239℃(ジクロロメタン-イソプロピルエーテル)。

NMR (DMSO-d6) δ 2.05(6H,s),6.46(2H,s),8.19(1H,s),9.13(1H,broad s),9.16(1H,s)。

【0141】参考例 6

1-アセトキシ-4-アセチルアミノ-2,3,5-トリメチルベンゼン

4-アミノ-2,3,5-トリメチルフェノール(26.5g, 17.5mmol)をピリジン(80ml)に溶かし、かき混ぜながら無水酢酸(53ml, 56.2mmol)を滴下した。反応液を1時間かき混ぜた後、氷水中に注ぎ析出した結晶をろ取した。結晶は水洗、乾燥後酢酸エチルから再結晶して目的物36.5g(収率 88.5%)を得た。融点 174-175℃。

NMR (CDCl3) δ 2.00-2.25(12H,m),2.31(3H,s),6.60-6.90(2H,m)。

【0142】参考例 7

1-アセトキシ-4-アセチルアミノ-2,3-ジメチルベンゼン

上記の方法に従って合成した。収率 88.3%。融点 155-156℃(ジクロロメタン-イソプロピルエーテル)。

NMR (CDCl3) δ 2.09(3H,s),2.14(3H,s),2.19(3H,s),2.33(2H,s),6.86(1H,d,J=8.5Hz),7.05(1H,broad s),7.37(1H,d,J=8.5Hz)。

【0143】参考例 8

1-アセトキシ-4-アセチルアミノ-2,5-ジメチルベンゼン

上記の方法に従って合成した。収率 54.9%。融点 177℃(ジクロロメタン-イソプロピルエーテル)。

NMR (CDCl3) δ 2.12(3H,s),2.16(3H,s),2.30(3H,s),6.81(1H,s),7.02(1H,broads),7.57(1H,s)。

【0144】参考例 9

4-アセチルアミノ-2,3,5-トリメチルフェノール

1-アセトキシ-4-アセチルアミノ-2,3,5-トリメチルベンゼン(66.0g, 324mmol)のメタノール(300ml)溶液に、炭

酸カリウム(27g, 195mmol)の水(150ml)溶液を加え、アルゴン雰囲気下室温で1時間かき混ぜた。反応液に1N-塩酸を加え弱酸性とした後、水で希釈した。析出した結晶をろ取し、水洗、乾燥後、酢酸エチル-イソプロピルエーテルから再結晶して目的物36.8g(収率 67.9%)を得た。融点189-190℃(酢酸エチル-イソプロピルエーテル)。

NMR (DMSO-d_6) δ 1.98(3H,s),1.99(6H,s),2.01(3H,s),6.50(1H,s),8.95(1H,s),9.00(1H,s)。

【０１４５】参考例 10

4-アセチルアミノ-2,3-ジメチルフェノール

上記の方法に従って合成した。収率 40.0%。融点 184-185℃(ジクロロメタン-イソプロピルエーテル)。

NMR ($CDCl_3$) δ 2.13(3H,s),2.16(3H,s),2.18(3H,s),6.66(1H,d,J=8.5Hz),7.01(1H,d,J=8.5Hz),7.22(1H,broad s),7.29(1H,s)。

【０１４６】参考例 11

4-アセチルアミノ-2,5-ジメチルフェノール

上記の方法に従って合成した。収率 92.1%。融点 183℃(ジクロロメタン-イソプロピルエーテル)。

NMR (DMSO-d_6) δ 1.97(3H,s),2.04(6H,s),6.58(1H,s),6.91(1H,s),9.03(2H,s)。

【０１４７】参考例 12

4-ホルミルアミノ-2,3,5-トリメチル-1-(2-メチル-2-プロペニルオキシ)ベンゼン

4-ホルミルアミノ-2,3,5-トリメチルフェノール(85.5g, 0.48mol)、塩化メタリル(45.3g, 0.5mol)のジメチルホルムアミド(300ml)溶液に炭酸カリウム(74.0g, 0.54mol)を加えてアルゴン雰囲気下80℃で3時間かき混ぜた。反応液は氷水中に注ぎ、析出した結晶をろ取し、水洗、乾燥した。得られた粗結晶はイソプロピルエーテルから再結晶して目的物 80.0g(収率 71.6%)を得た。融点144-145℃。

NMR ($CDCl_3$) δ 1.84(3H,m),2.17(3H,s),2.19(1.5H,s),2.22(3H,s),2.26(1.5H,s),4.40(1H,s),4.42(1H,s),4.99(1H,m),5.11(1H,broad s),6.60(1H,s),6.75(1H,m),7.98(0.5H,d,J=12.0Hz),8.41(0.5H,s)。

【０１４８】参考例 13

4-アセチルアミノ-2,3,5-トリメチル-1-(2-メチル-2-プロペニルオキシ)ベンゼン

上記の方法に従って合成した。収率 92.6%。融点 149-150℃(イソプロピルエーテル)。

NMR ($CDCl_3$) δ 1.84 and 1.86(3H,s),2.14(3H,s),2.16(3H,s),2.19(3H,s),2.20(3H,s),4.38 and 4.32(2H,s),4.98(1H,m),5.11(1H,broad s),6.58 and 6.50(1H,s),6.60 and 6.72(1H,broad s)。

【０１４９】参考例 14

2,3,5-トリメチル-1-(2-メチル-2-プロペニルオキシ)ベンゼン

上記の方法に従って合成した。収率 98.9%。沸点 108-112℃(10mmHg)。

NMR ($CDCl_3$) δ 1.87(3H,s),2.17(3H,s),2.26(3H,s),2.30(3H,s),4.42(2H,s),5.00(1H,broad s),5.15(1H,broad s),6.55(1H,broad s),6.64(1H,broad s)。

【０１５０】参考例 15

4-アセチルアミノ-2,3-ジメチル-1-(2-メチル-2-プロペニルオキシ)ベンゼン

上記の方法に従って合成した。収率 86.2%。融点 154-156℃(ジクロロメタン-イソプロピルエーテル)。

NMR ($CDCl_3$) δ 1.84(3H,s),2.16(3H,s),2.19(3H,s),2.21(3H,s),4.41(2H,s),4.98(1H,s),5.12(1H,s),6.70(1H,d,J=8.8Hz),6.89(1H,broad s),7.20(1H,d,J=8.8Hz)。

【０１５１】参考例 16

4-アセチルアミノ-2,5-ジメチル-1-(2-メチル-2-プロペニルオキシ)ベンゼン

上記の方法に従って合成した。収率 84.3%。融点 128-132℃(ジクロロメタン-イソプロピルエーテル)。

NMR ($CDCl_3$) δ 1.60 and 2.17(3H,s),1.84(3H,s),2.20(6H,s),4.40(2H,s),4.98(1H,s),5.11(1H,s),6.63(1H,s),6.80(1H,broad s),7.28(1H,s)。

【０１５２】参考例 17

4-ホルミルアミノ-3,5-ジメチル-1-(2-メチル-2-プロペニルオキシ)ベンゼン

上記の方法に従って合成した。収率 98.4%。融点 128-129℃(イソプロピルエーテル)。

NMR (DMSO-d_6) δ 1.77(3H,s),2.11(6H,s),4.43(2H,s),4.95(1H,s),5.05(1H,s),6.68(2H,s),8.22(1H,s),9.26(1H,s)。

【０１５３】参考例 18

4-ホルミルアミノ-3,5-ジメチル-2-(2-メチル-2-プロペニル)-1-(2-メチル-2-プロペニルオキシ)ベンゼン

上記の方法に従って合成した。収率 98.4%。融点：109℃(ジクロロメタン-イソプロピルエーテル)。

NMR (DMSO-d_6) δ 1.72(3H,s),1.76(3H,s),2.01(3H,s),2.12(3H,s),3.32(2H,s),4.30(1H,s),4.41(2H,s),4.66(1H,s),4.93(1H,s),5.06(1H,s),6.73(1H,s),8.22(1H,s),9.27(1H,s)。

【０１５４】参考例 19

4-ホルミルアミノ-2,3,5-トリメチル-6-(2-メチル-2-プロペニル)フェノール

4-ホルミルアミノ-2,3,5-トリメチル-1-(2-メチル-2-プロペニルオキシ)ベンゼン(80g, 0.34mol)をN,N-ジエチルアニリン(500ml)に溶かし、200℃で3時間加熱した。放冷し、結晶が析出し始めたらヘキサンを加え、析出した結晶をろ取し、目的物75.2g(収率 94.0%)を得た。粗結晶は酢酸エチル-イソプロピルエーテルから再結晶して融点 163-164℃の結晶を得た。

NMR ($CDCl_3$) δ 1.80(3H,s),2.16(3H,s),2.17(1.5H,s),2.19(1.5H,s),2.20(1.5H,s),2.21(1.5H,s),3.38(2H,broad s),4.65(1H,m),4.88(1H,m),5.16(0.5H,s),5.19(0.5H,s),6.70(1H,m),7.95(0.5H,d,J=12.0Hz),8.42(0.5H,d,

J=1.8Hz)。

【０１５５】参考例 20

4-アセチルアミノ-2,3,5-トリメチル-6-(2-メチル-2-プロペニル)フェノール

上記の方法に従って合成した。収率 97.7%。融点 209-210℃(酢酸エチル-イソプロピルエーテル)。

NMR (CDCl3) δ 1.73(3H,s),1.94(3H,s),1.99(6H,s),2.09(3H,s),3.33(2H,m),4.28(1H,broad s),4.64(1H,broad s),7.86(1H,broad s),9.00(1H,s)。

【０１５６】参考例 21

2,3,5-トリメチル-6-(2-メチル-2-プロペニル)フェノール

上記の方法に従って合成した。収率 80.6%。沸点 124-126℃(10mmHg)。

NMR (CDCl3) δ 1.79(3H,s),2.14(3H,s),2.24(6H,s),3.37(2H,s),4.74(1H,m),4.88(1H,m),5.08(1H,s),6.63(1H,s)。

【０１５７】参考例 22

4-アセチルアミノ-2,3-ジメチル-6-(2-メチル-2-プロペニル)フェノール

上記の方法に従って合成した。収率 91.8%。融点：149-151℃(ジクロロメタン-イソプロピルエーテル)。

NMR (CDCl3) δ 1.72(3H,s),2.12(3H,s),2.16(3H,s),2.17(3H,s),3.32(2H,s),4.89-4.94(2H,m),5.39(1H,s),6.92(1H,broad s),7.00(1H,s)。

【０１５８】参考例 23

4-アセチルアミノ-2,5-ジメチル-6-(2-メチル-2-プロペニル)フェノール

上記の方法に従って合成した。収率 98.7%。融点：183-185℃(ジクロロメタン-イソプロピルエーテル)。

NMR (CDCl3) δ 1.79(3H,s),2.11-2.22(9H,m),3.38(2H,s),4.60(1H,s),4.83(1H,s),7.11(1H,s)。

【０１５９】参考例 24

4-ホルミルアミノ-3,5-ジメチル-2-(2-メチル-2-プロペニル)フェノール

上記の方法に従って合成した。収率 80.8%。融点 207-209℃(イソプロピルエーテル)。

NMR (DMSO-d6) δ 1.71(3H,s),1.97(3H,s),2.04(3H,s),3.25(2H,s),4.33(1H,s),4.65(1H,s),6.55(1H,s),8.19(1H,s),9.09(1H,s)。

【０１６０】参考例 25

2,6-ビス(2-メチル-2-プロペニル)-4-ホルミルアミノ-3,5-ジメチルフェノール

上記の方法に従って合成した。収率 84.2%。融点 169-170℃(イソプロピルエーテル)。

NMR (DMSO-d6) δ 1.72(6H,s),1.98(6H,s),3.33(4H,s),4.28(2H,s),4.65(2H,s),7.86(1H,s),8.20(1H,s),9.19(1H,s)。

【０１６１】参考例 26

2-ブロモ-3,5,6-トリメチルアニソール

t-ブチルアミン (73g, 1.0mol)のトルエン(11)溶液を-20～30℃に冷却し、かき混ぜながら臭素(79.9g, 0.5mol)を約10分間で滴下した。次に反応液を-70～-75℃に冷却し、2,3,5-トリメチルフェノール(68g, 0.5mol)を最少量の塩化メチレンに溶かして滴下した。反応液は30分間同温度で、続いて3時間室温でかき混ぜた後、水で洗浄し、乾燥後濃縮した。別の反応器内に水素化ナトリウム(含有率60%, 22g, 0.55mol)を入れヘキサンで2～3回洗った後ジメチルホルムアミド(500ml)を加え、アルゴン雰囲気下、氷冷しながら先の濃縮残渣のジメチルホルムアミド(50ml)溶液を滴下した。反応液は30分間かき混ぜ、続いてヨードメタン(34.2ml, 0.55mol)を滴下し、さらに1時間かき混ぜた。反応液を水で希釈し、生成物をイソプロピルエーテルで抽出し、抽出液は、水洗、乾燥後濃縮した。濃縮残渣を減圧で蒸留して、沸点が130～135℃(10mmHg)の留分を集めると、目的物32.3g(収率28.6%)が得られた。

NMR (CDCl3) δ 2.20(3H,s),2.21(3H,s),2.34(3H,s),3.76(3H,s),6.83(1H,s)。

【０１６２】参考例 27

1-(2-メトキシ-3,4,6-トリメチルフェニル)-1-フェニル-2-メチルプロパノール

2-ブロモ-3,5,6-トリメチルアニソール(3.0g, 13.1mmol)のテトラヒドロフラン(20ml)溶液を-78℃に冷却し、n-ブチルリチウム(1.6Mヘキサン溶液, 8.2ml, 13.1mmol)を滴下した。反応液を同温度で15分間かき混ぜ、次にイソブチリルベンゼン(1.94g, 13.1mmol)のテトラヒドロフラン(5ml)溶液を滴下し、室温でさらに30分間かき混ぜた。反応液を水で希釈し、生成物をイソプロピルエーテルで抽出した。抽出液は水洗、乾燥後、濃縮し、残渣をヘキサンから結晶化させて、目的物3.13g(収率 80.2%)を得た。融点 80-81℃。

NMR (CDCl3) δ 0.88(3H,d,J=6.6Hz),1.05(3H,d,J=6.4Hz),2.07(3H,s),2.18(3H,s),2.58(3H,s),2.82(1H,qq,J=6.4Hz and 6.6Hz),2.90(3H,s),6.18(1H,broad s),6.75(1H,s),7.10-7.30(3H,m),7.40-7.50(2H,m)。

【０１６３】参考例 28

1-(4-フルオロフェニル)-1-(2-メトキシ-3,4,6-トリメチルフェニル)-2-メチルプロパノール

上記の方法に従って合成した。収率 97.9%。融点 102-103℃(ヘキサン)。

NMR (CDCl3) δ 0.88(3H,d,J=6.6Hz),1.02(3H,d,J=6.4Hz),2.08(3H,s),2.19(3H,s),2.53(3H,s),2.80(1H,qq,J=6.4Hz and 6.6Hz),2.97(3H,s),6.23(1H,broad s),6.75(1H,s),6.95(2H,t,J=8.8Hz),7.40(2H,dd,J=8.8 and 5.4Hz)。

【０１６４】参考例 29

1-(2-メトキシ-3,4,6-トリメチルフェニル)-1-(4-メチルフェニル)-2-メチルプロパノール

上記の方法に従って合成した。収率 80.6%。融点 103-1

04℃(ヘキサン)。
NMR (CDCl3) δ 0.89(3H,d,J=6.6Hz),1.03(3H,d,J=6.4Hz),2.09(3H,s),2.19(3H,s),2.30(3H,s),2.56(3H,s),2.82(1H,qq,J=6.4Hz and 6.6Hz),2.95(3H,s),6.18(1H,broad s),6.75(1H,s),7.07(2H,d,J=8.2Hz),7.32(2H,d,J=8.2Hz)。

【０１６５】参考例 30
1-(2-メトキシ-3,4,6-トリメチルフェニル)-1-(4-プロピルフェニル)-2-メチルプロパノール
上記の方法に従って合成した。収率 74.6%。融点 59-60℃(ヘキサン)。
NMR (CDCl3) δ 0.87(3H,t,J=6.4Hz),0.90(3H,d,J=6.6Hz),1.03(3H,d,J=6.4Hz),1.60(2H,sextet,6.4Hz),2.08(3H,s),2.18(3H,s),2.54(2H,t,J=6.4Hz),2.56(3H,s),2.84(1H,qq,J=6.6 and 6.4Hz),2.93(3H,s),6.15(1H,broad s),7.06(2H,d,J=8.4Hz),7.33(2H,d,J=8.4Hz)。

【０１６６】参考例 31
1-(2-メトキシ-3,4,6-トリメチルフェニル)-1-(4-ペンチルフェニル)-2-メチルプロパノール
上記の方法に従って合成した。収率 75.4%。融点 55-56℃(ヘキサン)。
NMR (CDCl3) δ 0.85(3H,t,J=6.2Hz),0.90(3H,d,J=6.6Hz),1.03(3H,d,J=6.6Hz),1.28(4H,m),1.56(2H,quintet,J=6.8Hz),2.08(3H,s),2.18(3H,s),2.54(2H,t,J=7.5Hz),2.55(3H,s),2.84(1H,septet,J=6.6Hz),2.92(3H,s),6.15(1H,broad s),6.75(1H,s),7.07(2H,d,J=8.0Hz),7.34(2H,d,J=8.0Hz)。

【０１６７】参考例 32
1-(4-イソプロピルフェニル)-1-(2-メトキシ-3,4,6-トリメチルフェニル)-2-メチルプロパノール
上記の方法に従って合成した。収率 65.1%。油状。
NMR (CDCl3) δ 0.91(3H,d,J=6.6Hz),1.02(3H,d,J=6.6Hz),1.20(6H,d,J=7.0Hz),2.08(3H,s),2.17(3H,s),2.54(3H,s),2.84(1H,septet,J=6.6Hz),2.93(3H,s),2.96(1H,septet,J=7.0Hz),6.16(1H,broad s),6.74(1H,s),7.10(2H,d,J=8.4Hz),7.90(2H,d,J=8.4Hz)。

【０１６８】参考例 33
1-(2-メトキシ-3,4,6-トリメチルフェニル)-1-(3-ピリジル)-2-メチルプロパノール
上記の方法に従って合成した。収率 68.9%。油状。
NMR (CDCl3) δ 0.93(3H,d,J=6.6Hz),1.03(3H,d,J=6.6Hz),2.09(3H,s),2.19(3H,s),2.51(3H,s),2.90(1H,septet,J=6.6Hz),3.05(3H,s),6.29(1H,broad s),6.76(1H,s),7.22(1H,dd,J=4.8Hz and 8.0Hz),7.79(1H,dt,J=2.0Hz and 8.0Hz),8.43(1H,dd,J=2.0Hz and 4.8Hz),8.70(1H,d,J=2.0Hz)。

【０１６９】参考例 34
1-(2-メトキシ-3,4,6-トリメチル)-1-(4-ジメチルアミノフェニル)-2-メチルプロパノール
上記の方法に従って合成した。収率 59.1%。融点 95-97℃(ヘキサン)。
NMR (CDCl3) δ 0.93(3H,d,J=6.6Hz),1.00(3H,d,J=6.4Hz),2.08(3H,s),2.18(3H,s),2.53(3H,s),2.82(1H,qq,J=6.4Hz and 6.6Hz),2.90(6H,s),2.99(3H,s),6.12(1H,broad s),6.66(2H,d,J=9.0Hz),6.74(1H,s),7.28(2H,d,J=9.0Hz)。

【０１７０】参考例 35
3-(2-メトキシ-3,4,6-トリメチルフェニル)-2,4-ジメチルペンタン-3-オール
上記の方法に従って合成した。収率 11.6%。油状。
NMR (CDCl3) δ 0.78(6H,d,J=6.6Hz),1.03(6H,d,J=6.6Hz),2.15(3H,s),2.19(3H,s),2.42(3H,s),2.45(2H,septet,J=6.6Hz),3.73(3H,s),6.75(1H,s),6.88(1H,s)。

【０１７１】参考例 36
5-アセチルアミノ-2,2,6,7-テトラメチル-2,3-ジヒドロベンゾフラン
実施例 3の方法に従って合成した。収率 71.9%。融点 163-164℃(エタノール)。
NMR (CDCl3) δ 1.45(6H,s),2.10(3H,s),2.11(3H,s),2.17(3H,s),2.98(2H,s),7.00(1H,s),7.33(1H,broad s)。

【０１７２】参考例 37
5-アセチルアミノ-2,2,4,7-テトラメチル-2,3-ジヒドロベンゾフラン
上記の方法に従って合成した。収率 67.3%。融点 161-162℃(イソプロピルエーテル)。
NMR (CDCl3) δ 1.47(6H,s),2.06(3H,s),2.13(3H,s),2.14(3H,s),2.93(2H,s),6.81(1H,broad s),6.95(1H,s)。

【０１７３】参考例 38
5-アミノ-2,2,4,6-テトラメチル-2,3-ジヒドロベンゾフラン塩酸塩
上記の方法に従って合成した。収率 43.0%。融点：215-217℃(イソプロパノール)。
NMR(DMSO-d6) δ 1.40(6H,s),2.22(3H,s),2.29(3H,s),2.94(2H,s),6.49(1H,s),9.58(2H,broad s)。

【０１７４】参考例 39
5-アミノ-2,2,6,7-テトラメチル-2,3-ジヒドロベンゾフラン塩酸塩
上記の方法に従って合成した。収率 38.7%。融点 235-238℃(エタノール)。
NMR (CDCl3) δ 1.45(6H,s),2.13(3H,s),2.40(3H,s),2.97(2H,s),7.27(2H,s),10.23(2H,broad s)。

【０１７５】参考例 40
2,2,4,6,7-ペンタメチル-3-フェニル-2,3-ジヒドロベンゾフラン
1-(2-メトキシ-3,4,6-トリメチルフェニル)-1-フェニル-2-メチルプロパノール(3.1g,10.4mmol)を48%臭化水素酸(20ml)に懸濁し、18時間加熱還流した。生成物はイソプロピルエーテルで抽出し、水洗、乾燥後濃縮した。残渣をエタノールから結晶化させ、目的物2.43g(収率 87.8%)を得た。融点 86-87℃。

NMR (CDCl3) δ 1.02(3H,s),1.51(3H,s),1.84(3H,s),2.15(3H,s),2.24(3H,s),4.13(1H,s),6.49(1H,s),6.70-7.40(5H,m)。

【０１７６】参考例 41

3-(4-フルオロフェニル)-2,2,4,6,7-ペンタメチル-2,3-ジヒドロベンゾフラン

上記の方法に従って合成した。収率 83.5%。融点 109-110℃(メタノール)。

NMR (CDCl3) δ 1.02(3H,s),1.49(3H,s),1.83(3H,s),2.14(3H,s),2.24(3H,s),4.10(1H,s),6.49(1H,s),6.60-7.20(4H,m)。

【０１７７】参考例 42

2,2,4,6,7-ペンタメチル-3-(4-メチルフェニル)-2,3-ジヒドロベンゾフラン

上記の方法に従って合成した。収率 87.7%。融点 117-118℃(メタノール)。

NMR (CDCl3) δ 1.02(3H,s),1.50(3H,s),1.85(3H,s),2.15(3H,s),2.24(3H,s),2.31(3H,s),4.10(1H,s),6.49(1H,s),6.50-7.20(4H,m)。

【０１７８】参考例 43

2,2,4,6,7-ペンタメチル-3-(4-プロピルフェニル)-2,3-ジヒドロベンゾフラン

上記の方法に従って合成した。収率 84.9%。融点 69-70℃(メタノール)。

NMR (CDCl3) δ 0.90(3H,t,J=7.2Hz),1.02(3H,s),1.50(3H,s),1.61(2H,sextet,J=8.0Hz),1.84(3H,s),2.15(3H,s),2.24(3H,s),2.55(2H,t,J=8.0Hz),4.10(1H,s),6.49(1H,s),6.60-7.20(4H,m)。

【０１７９】参考例 44

2,2,4,6,7-ペンタメチル-3-(4-ペンチルフェニル)-2,3-ジヒドロベンゾフラン

上記の方法に従って合成した。収率 70.7%。油状。

NMR (CDCl3) δ 0.88(3H,t,J=4.6Hz),1.03(3H,s),1.30(4H,m),1.50(3H,s),1.56(2H,m),1.85(3H,s),2.15(3H,s),2.24(3H,s),2.56(2H,t,J=8.0Hz),4.10(1H,s),6.45(1H,s),6.60-7.20(4H,m)。

【０１８０】参考例 45

3-(4-イソプロピルフェニル)-2,2,4,6,7-ペンタメチル-2,3-ジヒドロベンゾフラン

上記の方法に従って合成した。収率 65.1%。油状。

NMR (CDCl3) δ 1.02(3H,s),1.21(6H,d,J=7.0Hz),1.49(3H,s),1.84(3H,s),2.14(3H,s),2.24(3H,s),2.95(1H,septet,J=7.0Hz),4.09(1H,s),6.48(1H,s),6.70-7.20(4H,m)。

【０１８１】参考例 46

2,2,4,6,7-ペンタメチル-3-(3-ピリジル)-2,3-ジヒドロベンゾフラン

上記の方法に従って合成した。収率 77.1%。油状。

NMR (CDCl3) δ 1.05(3H,s),1.53(3H,s),1.84(3H,s),2.14(3H,s),2.24(3H,s),4.14(1H,s),6.50(1H,s),7.18(2H,m),8.35(1H,m),8.48(1H,t,J=3.2Hz)。

【０１８２】参考例 47

2,2,4,6,7-ペンタメチル-3-(4-ジメチルアミノフェニル)-2,3-ジヒドロベンゾフラン

上記の方法に従って合成した。収率 88.1%。融点 124-125℃(メタノール)。

NMR (CDCl3) δ 1.03(3H,s),1.48(3H,s),1.85(3H,s),2.14(3H,s),2.23(3H,s),2.91(6H,s),4.04(1H,s),6.47(1H,s),6.55-7.00(4H,m)。

【０１８３】参考例 48

3-(4-イソプロピル)-2,2,4,6,7-ペンタメチル-2,3-ジヒドロベンゾフラン

上記の方法に従って合成した。収率 88.2%。油状。

NMR (CDCl3) δ 0.73(3H,d,J=6.8Hz),0.98(3H,d,J=7.2Hz),1.21(3H,s),1.57(3H,s),2.06(3H,s),2.10(1H,m),2.20(3H,s),2.22(3H,s),2.73(1H,d,J=2.8Hz),6.49(1H,s)。

【０１８４】参考例 49

2,2,4,5,6-ペンタメチル-7-ニトロ-2,3-ジヒドロベンゾフラン

無水酢酸(5ml)と酢酸(5ml)の混合液を冷却し、かき混ぜながら注意深く硝酸(5ml)を加えた。次に2,2,4,5,6-ペンタメチル-2,3-ジヒドロベンゾフラン(2.9g, 13.9mmol)の無水酢酸(5ml)溶液を滴下し30分間かき混ぜた。反応液を氷水中に注ぎ、生成物を酢酸エチルで抽出した。抽出液は飽和炭酸水素ナトリウム水で洗浄し、乾燥後濃縮した。残渣をシリカゲルカラムクロマトグラフィー(ヘキサン-イソプロピルエーテル, 9:1)で精製し、メタノールから結晶化させて目的物0.35g(収率 9.8%)を得た。融点 100-101℃。

NMR (CDCl3) δ 1.51(6H,s),2.14(3H,s),2.17(3H,s),2.24(3H,s),2.99(2H,s)。

【０１８５】参考例 50

2,2,4,6,7-ペンタメチル-5-ニトロ-3-フェニル-2,3-ジヒドロベンゾフラン

無水酢酸(3ml)と酢酸(3ml)の混合液を冷却し、かき混ぜながら注意深く硝酸(3ml)を加えた。次に2,2,4,6,7-ペンタメチル-3-フェニル-2,3-ジヒドロベンゾフラン(3.7g, 13.9mmol)の無水酢酸(3ml)溶液を滴下し30分間かき混ぜた。反応液を氷水中に注ぎ、生成物を酢酸エチルで抽出した。抽出液は飽和炭酸水素ナトリウム水で洗浄し、乾燥後濃縮した。残渣をシリカゲルカラムクロマトグラフィー(ヘキサン-イソプロピルエーテル, 9:1)で精製し、メタノールから結晶化させて目的物2.08g(収率 48.1%)を得た。融点 155-156℃。

NMR (CDCl3) δ 1.04(3H,s),1.52(3H,s),1.83(3H,s),2.18(3H,s),2.20(3H,s),4.15(1H,s),6.85(2H,m),7.26(3H,m)。

【０１８６】参考例 51

3-(4-フルオロフェニル)-2,2,4,6,7-ペンタメチル-5-ニトロ-2,3-ジヒドロベンゾフラン

上記の方法に従って合成した。収率 66.3%。融点 94-95℃(メタノール)。
NMR ($CDCl_3$) δ 1.04(3H,s),1.50(3H,s),1.84(3H,s),2.18(3H,s),2.20(3H,s),4.14(1H,s),6.50-7.20(4H,m)。
【０１８７】参考例 52
2,2,4,6,7-ペンタメチル-3-(4-メチルフェニル)-5-ニトロ-2,3-ジヒドロベンゾフラン
上記の方法に従って合成した。収率 56.0%。油状。
NMR ($CDCl_3$) δ 1.05(3H,s),1.50(3H,s),1.84(3H,s),2.18(3H,s),2.20(3H,s),2.32(3H,s),4.11(1H,s),6.50-7.20(4H,m)。
【０１８８】参考例 53
2,2,4,6,7-ペンタメチル-5-ニトロ-3-(4-プロピルフェニル)-2,3-ジヒドロベンゾフラン
上記の方法に従って合成した。収率 65.8%。油状。
NMR ($CDCl_3$) δ 0.91(3H,t,J=7.4Hz),1.04(3H,s),1.50(3H,s),1.61(2H,sextet,J=7.4Hz),1.84(3H,s),2.18(3H,s),2.20(3H,s),2.55(2H,t,J=7.4Hz),4.12(1H,s),6.50-7.20(4H,m)。
【０１８９】参考例 54
2,2,4,6,7-ペンタメチル-5-ニトロ-3-(4-ペンチルフェニル)-2,3-ジヒドロベンゾフラン
上記の方法に従って合成した。収率 76.4%。油状。
NMR ($CDCl_3$) δ 0.89(3H,t,J=6.6Hz),1.04(3H,s),1.30(4H,m),1.50(3H,s),1.59(2H,m),1.84(3H,s),2.18(3H,s),2.20(3H,s),2.56(2H,t,J=7.8Hz),4.11(1H,s),5.50-7.20(4H,m)。
【０１９０】参考例 55
3-(4-イソプロピルフェニル)-2,2,4,6,7-ペンタメチル-5-ニトロ-2,3-ジヒドロベンゾフラン
上記の方法に従って合成した。収率 48.0%。融点 109-110℃(メタノール)。
NMR ($CDCl_3$) δ 1.04(3H,s),1.22(6H,d,J=6.8Hz),1.50(3H,s),1.84(3H,s),2.18(3H,s),2.20(3H,s),2.87(1H,septet,J=6.8Hz),4.12(1H,s),6.60-7.20(4H,m)。
【０１９１】参考例 56
2,2,4,6,7-ペンタメチル-5-ニトロ-3-(3-ピリジル)-2,3-ジヒドロベンゾフラン
上記の方法に従って合成した。収率 60.7%。油状。
NMR ($CDCl_3$) δ 1.07(3H,s),1.54(3H,s),1.84(3H,s),2.19(3H,s),2.21(3H,s),4.18(1H,s),7.05-7.35(2H,m),8.25-8.60(2H,m).
【０１９２】参考例 57
2,2,4,6,7-ペンタメチル-3-(4-ジメチルアミノ-3-ニトロフェニル)-5-ニトロ-2,3-ジヒドロベンゾフラン
上記の方法に従って合成した。収率 24.2%。油状。
NMR ($CDCl_3$) δ 1.13(3H,s),1.51(3H,s),1.91(3H,s),2.19(3H,s),2.21(3H,s),2.81(6H,s),4.12(1H,s),7.00-7.80(3H,m)。
【０１９３】参考例 58
3-イソプロピル-2,2,4,6,7-ペンタメチル-5-ニトロ-2,3-ジヒドロベンゾフラン
上記の方法に従って合成した。収率 62.0%。油状。
NMR ($CDCl_3$) δ 0.72(3H,d,J=7.0Hz),0.98(3H,d,J=7.2Hz),1.23(3H,s),1.59(3H,s),2.09(1H,m),2.10(3H,s),2.16(3H,s),2.21(3H,s),2.78(1H,d,J=2.8Hz)。
【０１９４】参考例 59
2,4,6,7-テトラメチル-5-ニトロ-2-ピペリジノメチル-2,3-ジヒドロベンゾフラン
上記の方法に従って合成した。収率 62.8%。油状。
NMR ($CDCl_3$) δ 1.30-1.60(6H,m),1.42(3H,s),2.08(3H,s),2.14(6H,s),2.50(6H,m),2.78(1H,d,J=15.6Hz),3.18(1H,d,J=15.6Hz)。
【０１９５】参考例 60
2,4,6,7-テトラメチル-2-モルフォリノメチル-5-ニトロ-2,3-ジヒドロベンゾフラン
上記の方法に従って合成した。収率 59.0%。油状。
NMR ($CDCl_3$) δ 1.44(3H,s),2.07(3H,s),2.15(6H,s),2.57(6H,m),2.80(1H,d,J=15.6Hz),3.21(1H,d,J=15.6Hz),3.66(4H,t,J=4.4Hz)。
【０１９６】参考例 61
2,4,6,7-テトラメチル-2-[2-(ジメチルアミノ)エチル]-5-ニトロ-2,3-ジヒドロベンゾフラン
上記の方法に従って合成した。収率 53.0%。油状。
NMR ($CDCl_3$) δ 1.44(3H,s),1.62(2H,m),2.10(3H,s),2.13(3H,s),2.15(3H,s),2.24(6H,s),2.40(2H,m),2.87(1H,d,J=15.6Hz),3.06(1H,d,J=15.6Hz)。
【０１９７】参考例 62
2,4,6,7-テトラメチル-5-ニトロ-2-(2-ピペリジノエチル)-2,3-ジヒドロベンゾフラン
上記の方法に従って合成した。収率 46.3%。融点 247-250℃。
NMR ($CDCl_3$) δ 1.50(3H,s),1.90(2H,m),2.08(3H,s),2.13(3H,s),2.14(3H,s),2.18(4H,m),2.40(2H,m),2.64(2H,m),2.97(1H,d,J=15.6Hz),3.07(2H,m),3.17(1H,d,J=15.6Hz),3.55(2H,m)。
【０１９８】参考例 63
2,2,4,5,6-ペンタメチル-2,3-ジヒドロベンゾフラン
3,4,5-トリメチルフェノール(5.0g, 36.7mmol)、2-メチル-2-プロペノール(3.2g,44.0mmol)をギ酸(50ml)中に加え、3時間加熱還流した。反応液はイソプロピルエーテルで希釈し、水及び飽和炭酸水素ナトリウム水で洗浄し、乾燥後濃縮した。残渣をシリカゲルカラムクロマトグラフィー(ヘキサン-イソプロピルエーテル、97:3)で精製して、目的物2.9g(41.5%)を得た。油状。
NMR ($CDCl_3$) δ 1.45(6H,s),2.09(3H,s),2.14(3H,s),2.23(3H,s),2.93(2H,s),6.44(1H,s)。
【０１９９】参考例 64
5-ブロモ-2-ブロモメチル-2,4,6,7-テトラメチル-2,3-ジヒドロベンゾフラン

実施例29の方法に従って合成した。収率 67.7%。融点 60-61℃(メタノール)。
NMR (CDCl3) δ 1.61(3H,s),2.15(3H,s),2.27(3H,s),2.35(3H,s),2.67(1H,d,J=15.6Hz),3.33(1H,d,J=15.6Hz),3.51(2H,s)。

【０２００】参考例 65
2-ブロモメチル-2,4,6,7-テトラメチル-2,3-ジヒドロベンゾフラン
5-ブロモ-2-ブロモメチル-2,4,6,7-テトラメチル-2,3-ジヒドロベンゾフラン(12.4g, 35.6mmol)のエタノール(100ml)溶液にトリエチルアミン(5.0ml, 35.6mmol)を加え、5%-パラジウム炭素(5g)上、水素雰囲気下で接触水素化分解反応を行った。反応終了後、触媒をろ去し、ろ液を濃縮した。残渣をイソプロピルエーテルに溶かし、水洗、乾燥後溶媒を留去した。残渣をメタノールから結晶化させて目的物8.84g(収率 92.2%)を得た。融点 39-40℃。
NMR (CDCl3) δ 1.63(3H,s),2.08(3H,s),2.17(3H,s),2.21(3H,s),2.92(1H,d,J=15.8Hz),3.26(1H,d,J=15.8Hz),3.48(1H,d,J=15.6Hz),3.58(1H,d,J=15.6Hz),6.53(1H,s)。

【０２０１】参考例 66
2,4,6,7-テトラメチル-2-ピペリジノメチル-2,3-ジヒドロベンゾフラン
実施例57の方法に従って合成した。収率 81.6%。油状。
NMR (CDCl3) δ 1.30-1.60(6H,m),1.44(3H,s),2.05(3H,s),2.15(3H,s),2.19(3H,s),2.40-2.65(6H,m),2.76(1H,d,J=15.2Hz),3.06(1H,d,J=15.2Hz),6.47(1H,s)。

【０２０２】参考例 67
2,4,6,7-テトラメチル-2-モルフォリノメチル-2,3-ジヒドロベンゾフラン
上記の方法に従って合成した。収率 99.8%。油状。
NMR (CDCl3) δ 1.44(3H,s),2.04(3H,s),2.15(3H,s),2.19(3H,s),2.40-2.70(6H,m),2.79(1H,d,J=15.4Hz),3.08(1H,d,J=15.4Hz),3.67(4H,t,J=4.6Hz),6.48(1H,s)。

【０２０３】参考例 68
2-シアノメチル-2,4,6,7-テトラメチル-2,3-ジヒドロベンゾフラン
2-ブロモメチル-2,4,6,7-テトラメチル-2,3-ジヒドロベンゾフラン(6.5g,18.6mmol)をジメチルスルホキシド(30ml)に溶かし、シアン化ナトリウム(1.43g,88mmol)を加えて80℃で18時間かき混ぜた。反応液は水で希釈し、生成物を酢酸エチルで抽出した。抽出液を水洗、乾燥後濃縮し、残渣をシリカゲルカラムクロマトグラフィー(ヘキサン-イソプロピルエーテル、2:1)で精製した。得られた粗結晶をメタノールから再結晶して目的物4.1g(収率 79.7%)を得た。融点 58-59℃。
NMR (CDCl3) δ 1.66(3H,s),2.07(3H,s),2.16(3H,s),2.20(3H,s),2.68(1H,d,J=10.8Hz),2.75(1H,d,J=10.8Hz),3.00(1H,d,J=15.8Hz),3.12(1H,d,J=15.8Hz),6.54(1H,s)。

【０２０４】参考例 69
2,4,6,7-テトラメチル-2,3-ジヒドロベンゾフラン-2-イル酢酸
2-シアノメチル-2,4,6,7-テトラメチル-2,3-ジヒドロベンゾフラン(6.9g,32.1mmol)のメタノール(30ml)溶液に、水酸化ナトリウム(12.0g,300mmol)の水(30ml)溶液を加えて18時間加熱還流した。反応液は6N-塩酸で弱酸性とし、生成物を酢酸エチルで抽出した。抽出液を水洗、乾燥後濃縮し、残渣を酢酸エチル-ヘキサンから結晶化させて目的物6.0g(収率 79.9%)を得た。融点139-140℃。
NMR (DMSO-d6) δ 1.61(3H,s),2.07(3H,s),2.16(3H,s),2.21(3H,s),2.78(1H,d,J=10.8Hz),2.85(1H,d,J=10.8Hz),2.97(1H,d,J=15.4Hz),3.21(1H,d,J=15.4Hz),6.52(1H,s),8.50(1H,broad s)。

【０２０５】参考例 70
N,N-ジメチル-2,4,6,7-テトラメチル-2,3-ジヒドロベンゾフラン-2-イルアセトアミド
2,4,6,7-テトラメチル-2,3-ジヒドロベンゾフラン-2-イル 酢酸(3.0g,12.8mmol)のジメチルホルムアミド(30ml)溶液に1-ヒドロキシ-1H-ベンゾトリアゾール 1水和物(HOBt)(2.1g,14.1mmol)と1-エチル-3-(3-ジメチルアミノプロピル)カルボジイミド塩酸塩(WSC)(3.7g,19.2mmol)とを加え、室温で1時間かき混ぜた。次に50%ジメチルアミン水溶液(3ml)を加え、さらに30分間かき混ぜた。反応液は水で希釈し、生成物を酢酸エチルで抽出した。抽出液を水洗、乾燥後濃縮し、残渣をシリカゲルカラムクロマトグラフィー(イソプロピルエーテル)で精製して目的物3.1g(収率 92.6%)を得た。油状。NMR (CDCl3) δ 1.59(3H,s),2.07(3H,s),2.14(3H,s),2.20(3H,s),2.77(1H,d,J=15.0Hz),2.88(1H,d,J=15.0Hz),2.94(3H,s),3.00(1H,d,J=15.8Hz),3.03(3H,s),3.27(1H,d,J=15.8Hz),6.50(1H,s)。

【０２０６】参考例 71
(2,4,6,7-テトラメチル-2,3-ジヒドロベンゾフラン-2-イル)アセチル-1-ピペリジン
上記の方法に従って合成した。収率 90.7%。油状。
NMR (CDCl3) δ 1.55(3H,s),1.60(6H,m),2.06(3H,s),2.13(3H,s),2.19(3H,s),2.78(1H,d,J=14.8Hz),2.90(1H,d,J=14.8Hz),2.97(1H,d,J=15.8Hz),3.24(1H,d,J=15.8Hz),3.40-3.60(4H,m),6.50(1H,s)。

【０２０７】参考例 72
2,4,6,7-テトラメチル-2-[2-(ジメチルアミノ)エチル]-2,3-ジヒドロベンゾフラン
N,N-ジメチル-2.4.6.7-テトラメチル-2,3-ジヒドロベンゾフラン-2-イルアセトアミド(3.1g, 11.9mmol)をテトラヒドロフラン(50ml)に溶かし、冷却しながら水素化アルミニウムリチウム(0.45g)を少しづつ加えた。反応液は30分間室温でかき混ぜた後、氷水中に注いだ。生成物を酢酸エチルで抽出し、抽出液は水洗乾燥後、濃縮し

た。残渣をシリカゲルカラムクロマトグラフィー(クロロホルム-メタノール、95:5)で精製し、目的物2.2g(収率 81.6%)を得た。油状。
NMR (CDCl3) δ 1.42(3H,s),1.90(2H,m),2.06(3H,s),2.12(3H,s),2.19(3H,s),2.23(6H,s),2.40(2H,m),2.82(1H,d,J=15.4Hz),3.00(1H,d,J=15.4Hz),6.47(1H,s)。

【０２０８】参考例 73
2,4,6,7-テトラメチル-2-(2-ピペリジノエチル)-2,3-ジヒドロベンゾフラン
上記の方法に従って合成した。収率 74.9%。油状。
NMR (CDCl3) δ 1.42(3H,s),1.30-1.60(6H,m),1.90(2H,m),2.05(3H,s),2.12(3H,s),2.21(3H,s),2.40-2.60(6H,m),2.82(1H,d,J=15.8Hz),3.00(1H,d,J=15.8Hz),6.47(1H,s)。

【０２０９】参考例 74
4-(4-クロロフェニルミノ)-3,5,6-トリメチル-2-(2-メチル-2-プロペニル)-2,5-シクロヘキサジエン-1-オン
ピリジン(7.13ml、88.2mmol)の1,2-ジクロロエタン(40ml)溶液に、四塩化チタン(2.42ml、22.1mmol)を滴下し、滴下終了後反応液をアルゴン雰囲気下にて20分間加熱還流した。反応液を冷却した後、これに3,5,6-トリメチル-2-2-メチル-2-プロペニル)-1,4-ベンゾキノン(3.00g、14.7mmol)およびp-クロロアニリン(5.62g、44.1mmol)の1,2-ジクロロエタン(20ml)溶液を加え、混合物をアルゴン雰囲気下、90℃で45分間撹拌した。反応液を冷却した後、セライトろ過し、ろ液を飽和食塩水で洗浄後、乾燥、濃縮した。残渣をシリカゲルカラムクロマトグラフィー(ヘキサン-酢酸エチル、93:7)で精製し、目的物4.43g(収率 96.0%)を得た。油状。
NMR (CDCl3) δ 1.53-2.20(12H,m),3.21(2H,s),4.51(1H,s),4.74(1H,s),6.68(2H,d,J=8.8Hz),7.30(2H,d,J=8.8Hz)。

【０２１０】参考例 75
4-(4-メトキシフェニルイミノ)-3,5,6-トリメチル-2-(2-メチル-2-プロペニル) -2,5-シクロヘキサジエン-1-オン
参考例74と同様の方法に従って合成した。収率 19.1%。油状。
NMR (CDCl3) δ 1.50-1.60(3H,m),1.77(3H,broad s),1.95-2.03(3H,m),2.25(3H,broad s),3.16-3.25(2H,m),3.82(3H,s),4.46-4.58(1H,m),4.74(1H,broad s),6.72(2H,d,J=9.0Hz),6.88(2H,d,J=9.0Hz)。

【０２１１】参考例 76
4-(4-クロロフェニルアミノ)-3,5,6-トリメチル-2-(2-メチル-2-プロペニル)フェノール
4-(4-クロロフェニルイミノ)-3,5,6-トリメチル-2-(2-メチル-2-プロペニル)-2,5-シクロヘキサジエン-1-オン(4.40g、14.0mmol)のテトラヒドロフラン(20ml)溶液に、ハイドロサルファイトナトリウム(24.4g、0.14mol)の水(50ml)溶液を加え、室温で30分間撹拌した。有機層を分取した後、水層を酢酸エチルで抽出した。抽出液と有機層を合わせ、これを水洗、乾燥した後、溶媒を減圧下留去した。残渣をシリカゲルカラムクロマトグラフィー(ヘキサン-酢酸エチル、95:5)で精製し、目的物4.30g(収率 97.2%)を得た。油状。
NMR (CDCl3) δ 1.80(3H,s),2.11(3H,s),2.12(3H,s),2.19(3H,s),3.40(2H,s),4.68(1H,s),4.87(1H,s),5.04(1H,s),5.14(1H,broad s),6.34(2H,d,J=8.8Hz),7.06(2H,d,J=8.8Hz)。

【０２１２】参考例 77
4-(4-メトキシフェニルアミノ)-3,5,6-トリメチル-2-(2-メチル-2-プロペニル) フェノール
参考例74と同様の方法に従って合成した。収率 98.2%。油状。
NMR (CDCl3) δ 1.80(3H,s),2.14(6H,s),2.19(3H,s),3.40(2H,s),3.73(3H,s),4.69(1H,s),4.85-5.05(3H,m),6.38(2H,d,J=8.8Hz),6.73(2H,d,J=8.8Hz)。

【０２１３】参考例 78
3,5,6-トリメチル-2-(2-メチル-2-プロペニル)-4-フェニルアミノフェノール
ピリジン(7.60ml、93.6mmol)の1,2-ジクロロエタン(40ml)溶液に、四塩化チタン(2.58ml、23.4mmol)を滴下し、滴下終了後反応液をアルゴン雰囲気下にて30分間加熱還流した。反応液を冷却した後、これに3,5,6-トリメチル-2-(2-メチル-2-プロペニル)-1,4-ベンゾキノン(2.40g、11.7mmol)およびアニリン(3.35ml、35.1mmol)の1,2-ジクロロエタン(5ml)溶液を加え、混合物をアルゴン雰囲気下、90℃で2時間撹拌した。反応液を冷却した後、セライトろ過し、ろ液を減圧下濃縮した。残渣をシリカゲルカラムクロマトグラフィー(ヘキサン-酢酸エチル、98:2)で精製した。得られた化合物のテトラヒドロフラン(10ml)溶液に、ハイドロサルファイトナトリウム(12g、69mmol)の水(30ml)溶液を加え、室温で30分間撹拌した。有機層を分取した後、水層を酢酸エチルで抽出した。抽出液と有機層を合わせ、これを水洗、乾燥後、溶媒を減圧下留去した。残渣をシリカゲルカラムクロマトグラフィー(ヘキサン-酢酸エチル、95:5)で精製し、目的物1.41g(収率 42.8%)を得た。油状。
NMR (CDCl3) δ 1.80(3H,s),2.14(6H,s),2.19(3H,s),3.41(2H,s),4.69(1H,s),4.87(1H,s),5.03(1H,s)5.11,(1H,broad s),6.42(2H,d,J=7.4Hz),6.68(1H,t,J=7.4Hz),7.13(2H,t,J=7.4Hz)。

【０２１４】試験例１
塩化第１鉄マウス脊髄くも膜下腔内投与による行動変化に対する薬物の作用１群１０匹の５週令雄性ＳＩc:ＩＣＲマウスを使用した。５０mM塩化第１鉄を溶解した生理的食塩水５μl／マウスを第６腰髄から第１仙髄のくも膜下腔内に注入した後、１５分から１時間まで行動観察を行い、行動変化の評点は以下の基準で行った。
評点　　行動変化

０点：正常
１点：下肢、下腹部をしきりに噛む。
２点：a)激しく時には転げ回りながら下半身を噛む。
b)外部刺激に対する過敏反応が認められ、攻撃的になる。
c)振顔が起こる。
以上３つの反応のいずれかが認められる。
３点：間代性痙攣が認められる。
４点：強直性痙攣が認められる。もしくは片側または両側肢の麻痺が認められる。
５点：死亡する。
以上の基準で評価した点数をもとに抑制率で示した。被験化合物は塩化第１鉄投与３０分間に経口投与した。化合物[Ｉ]をそれぞれ１００mg／kg経口投与したときの平均スコアーおよびそれぞれの抑制率を表１に示す。
【表１】

化合物実施例No.	平均スコアー		抑制率（%）
	100mg／kg投与	生理食塩水投与	
103	0.1	4.9	98.0
1	1.2	4.6	73.9
84	0.5	4.6	89.1
47	1.0	4.9	79.6
85	0.6	4.6	87.0

以上の結果から、本発明化合物は塩化第１鉄による過酸化脂質生成に伴う中枢神経系障害の抑制作用がすぐれていることがわかる。
【０２１５】
【発明の効果】本発明化合物[Ｉ]は、前記試験例でも示されるように過酸化脂質生成抑制作用(抗酸化作用)、リポキシゲナーゼおよびＨＨＴの生成阻害または抑制作用等を有し、循環器系疾患、炎症、アレルギー疾患等の治療や予防のための医薬として有用である。

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